THE USE OF CD40 INHIBITORS FOR INHIBITING AN IMMUNE RESPONSE AND ENABLING IMMUNOGEN ADMINISTRATION AND RE-ADMINISTRATION

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Application No. 63/560,328, filed March 1, 2024, U.S. Provisional Application No. 63/660,285, filed June 14, 2024, and U.S. Provisional Application No. 63/733,566, filed December 13, 2024, each of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on February 28, 2025, is named 250298_000809_SL.xml and is 446,588 bytes in size.

FIELD OF THE INVENTION

[003] The present disclosure provides compositions and methods for inhibiting an immune response to an immunogen (e.g., an immunogenic delivery vehicle) in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor, e.g., an antigen-binding molecule that binds to CD40 (e.g., an anti-CD40xCD40 bispecific antibody, or a functional fragment thereof).

BACKGROUND

[004] Recombinant vectors including recombinant viral vectors (e.g., adeno-associated virus (AAV) vectors) are promising therapeutics which have been widely used in various applications such as gene therapy. Unfortunately, induced or pre-existing host immunity against potentially immunogenic gene delivery vectors (e.g., AAVs), e.g., immune responses involving B cell production of neutralizing antibodies (nAbs) against, e.g., capsids, and/or transgene products, can hinder the effectiveness of these therapeutics, particularly in instances requiring repeated gene delivery treatment (i.e., re-dosing of recombinant vector-based therapeutics). Indeed, rapid generation of anti-vector (e.g., AAV vector) antibodies can prevent re-dosing and neutralizing titers may persist for 15 years following initial treatment. T cell immune responses to vectors can also cause loss of efficacy over time that cannot be easily recovered due to the inability to re-dose. Immune responses also pose challenges for safe treatment using gene delivery vectors.

There are also numerous clinical holds due to immune-related serious adverse events (SAEs), such as thrombotic microangiopathy, hepatic injury/acute liver failure, and myositis.

[005] Natural AAVs are generally considered non-pathogenic and are capable of infecting a broad range of human tissues and organs; however, AAV infection can induce humoral and cellular immune responses. On average, 30-60% of individuals can have pre-existing anti-AAV nAbs from exposure to naturally occurring AAVs. For AAV8, in particular, it has been estimated that nearly 30-40% of the US population harbor pre-existing antibodies from natural AAV exposure, an estimate which can be much higher for other geographic locations or based on individual demographics, thereby limiting the eligibility of such individuals for AAV8-based treatments due to the ability of these antibodies to block transduction at relatively low titers. Additionally, exposure to AAV vectors in gene therapy induces potent nAbs that are generally high titer, serotype cross-reactive, and long-lived, persisting in some cases for at least a decade. These nAbs from a first AAV administration have been shown to inhibit transgene expression on subsequent AAV re-administration(s), thereby limiting the ability to re-dose in scenarios of transgene loss (e.g. from a T cell immune response or AAV episome loss over time) or a subtherapeutic initial dose. In addition to antibody responses against AAV capsid, antibody responses against the encoded transgene protein can also contribute to reductions in therapeutic efficacy.

[006] CD40 is a cell surface receptor that is part of the tumor necrosis factor (TNF) receptor superfamily. CD40 is expressed on antigen-presenting cells such as B cells, macrophages, and dendritic cells, as well as some non-immune cells and tumors (Dakal et al, *Immunobiology* 2020, 225:151899). The interaction of CD40 with its ligand CD40L provides a co-stimulatory signal that is essential to the survival of many cell types and is required for functions of immune response such as B cell activation (particularly in response to T-dependent antigens), germinal center formation and selection, development of long-lived plasma cells and memory B cells responses, IgG class switching, and "licensing" of dendritic cells to mature and become more potent inducers of T-cell immunity (see, e.g., Kawabe et al., *Immunity* 1994, 1:167-178; Elgueta et al., *Immunol. Rev.* 2009, 229:152-172).

[007] CD40-CD40L signaling is implicated in autoimmune conditions that are largely driven by autoantibodies, such as systemic rheumatic diseases where autoantibodies play an important role in disease progression (such as multiple sclerosis, autoimmune nephritis, rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus) as well as non-rheumatic conditions having an autoantibody component (such as myasthenia gravis, Grave's disease, and neuromyelitis optica) (see, Karnell et al., *Adv Drug Delivery Rev.* 2019, 141:92-

103). Altered CD40-CD40L signaling is also implicated in other diseases and conditions such as cardiovascular disease and transplantation (see, e.g., Dakal et al, *Immunobiology* 2020, 225:151899; Pamukcu et al., *Ann. Med.* 2011, 43:331; 340; Pinelli et al., *Immunotherapy* 2015, 7:399-410).

SUMMARY

[008] As specified in the Background section above, there exists a need in the art to enhance the efficacy of treatments with, e.g., recombinant vectors (e.g., AAV). This can be achieved, e.g., by inhibiting an immune response against such recombinant vectors and/or their transgene products (e.g., therapeutic polypeptides or polynucleotides encoded by the transgene), thereby improving efficacy and reducing toxicity of gene therapy. Such advancements would allow for stepwise dosing and/or effective re-administration (i.e., re-dosing) of the recombinant vectors (e.g., AAV) to increase or maintain the level of a transgene expression. The present disclosure addresses these and other needs.

[009] In one aspect, provided herein is a method for inhibiting an immune response to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

[010] In some embodiments, inhibiting the immune response comprises suppression of numbers and/or frequencies of immunogen-specific B cells.

[011] In some embodiments, inhibiting the immune response comprises suppression of immunogen-specific IgG and/or IgM responses.

[012] In certain embodiments, inhibiting the immune response comprises suppression of numbers and/or frequencies of follicular T helper cells (TFH) and/or CD4+ T cells.

[013] In one embodiment, inhibiting the immune response comprises suppression of immunogen-specific IFNγ responses.

[014] In some embodiments, inhibiting the immune response comprises suppression of magnitude and/or duration of the immune response.

[015] In another aspect, provided herein is a method for inhibiting generation of neutralizing antibodies to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

[016] In another aspect, provided herein is a method for preventing and/or suppressing an immunogen-specific T cell response in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

[017] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises suppression of numbers and/or frequencies of the immunogen-specific T cells.

[018] In some embodiments, the immunogen-specific T cells comprise follicular T helper cells (TFH) and/or CD4+ T cells.

[019] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or a tissue in the subject in response to the immunogen.

[020] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle, and the prevention and/or suppression of the immunogen-specific T cell response comprises increasing or maintaining the level of transgene expression in the subject.

[021] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or tissue in the subject in response to transgene expression in the organ and/or a tissue.

[022] In some embodiments, the tissue is muscle.

[023] In some embodiments, the organ is liver.

[024] In a further aspect, provided herein is a method for increasing effectiveness of re-administration of an immunogen to a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

[025] In some embodiments, the immunogen re-administration occurs via the same administration route as its prior administration.

[026] In some embodiments, the immunogen re-administration occurs via a different administration route than its prior administration.

[027] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[028] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[029] In certain embodiments, the CD40 inhibitor is administered before the administration of the immunogen to the subject.

[030] In certain embodiments, the CD40 inhibitor is administered simultaneously with the administration of the immunogen to the subject.

[031] In certain embodiments, the CD40 inhibitor is administered after the administration of the immunogen to the subject.

[032] In certain embodiments, the immunogen is administered to the subject two or more times and the CD40 inhibitor is administered before and/or between each of the administrations of the immunogen.

[033] In some embodiments, the subject has a preexisting immune response to the immunogen.

[034] In some embodiments, the method further comprises administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogen.

[035] In some embodiments, the method further comprises administering to the subject an immunoglobulin depleting agent.

[036] In some embodiments, the immunoglobulin depleting agent is administered before the administration of the CD40 inhibitor to the subject, and the CD40 inhibitor is administered before the administration of the immunogen to the subject.

[037] In some embodiments, the CD40 inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, and the immunoglobulin depleting agent is administered before the administration of the immunogen to the subject.

[038] In some embodiments, the CD40 inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject has preexisting immunity against the immunogen.

[039] In some embodiments, the CD40 inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject does not have preexisting immunity against the immunogen.

[040] In some embodiments, the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40 inhibitor is resistant to said immunoglobulin degrading enzyme.

[041] In some embodiments, the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, and HNSA-5487.

[042] In some embodiments, the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

[043] In some embodiments, the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

[044] In some embodiments, the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen

receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

[045] In some embodiments, the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

[046] In some embodiments, the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

[047] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[048] In some embodiments, the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[049] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[050] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3

comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[051] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[052] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[053] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[054] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[055] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[056] In some embodiments, the method further comprises administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogen.

[057] In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

[058] In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[059] In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[060] In some embodiments, the B cell depleting agent is an agent that binds to a B cell surface molecule.

[061] In some embodiments, the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

[062] In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

[063] In some embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

[064] In some embodiments, the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

[065] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[066] In some embodiments, the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[067] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[068] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[069] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[070] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[071] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[072] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[073] In some embodiments, the B cell depleting agent is an agent targeting a B cell survival factor.

[074] In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

[075] In some embodiments, the immunoglobulin depleting agent is capable of accelerating IgG clearance.

[076] In some embodiments, the immunoglobulin depleting agent is a neonatal fragment crystallizable (Fc) receptor (FcRn) blocker.

[077] In some embodiments, the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

[078] In some embodiments, the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

[079] In some embodiments, the plasma cell depleting agent is administered simultaneously with the immunogen, prior to the immunogen, or prior to and after the immunogen,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogen and the plasma cell depleting agent is administered if the immunogen is still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogen.

[080] In some embodiments, the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent is administered prior to the CD40 inhibitor.

[081] In some embodiments, the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent and the CD40 inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogen when the plasma cell depleting agent and the CD40 inhibitor are administered.

[082] In some embodiments,

(I) the subject does not have preexisting immunity against the immunogen before administration of a first dose of the immunogen, the CD40 inhibitor is administered prior to the first dose of the immunogen, the subject develops immunity against the immunogen from the first dose of the immunogen, and the plasma cell depleting agent is administered after the first dose of the immunogen but prior to a second dose of the immunogen; or

(II) the subject does not have preexisting immunity against the immunogen before administration of the immunogen, the CD40 inhibitor is administered prior to the immunogen, the subject develops immunity against the immunogen from the

administration of the immunogen, and the plasma cell depleting agent is administered after the immunogen but prior to administration of a second immunogen.

[083] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[084] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[085] In one embodiment, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[086] In some embodiments, the immunogen is an immunoglobulin depleting agent.

[087] In some embodiments, the immunoglobulin depleting agent is administered before the administration of the CD40 inhibitor to the subject at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

[088] In some embodiments, the immunoglobulin depleting agent is administered before the administration of the CD40 inhibitor to the subject at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

[089] In some embodiments, the CD40 inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

[090] In some embodiments, the CD40 inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

[091] In some embodiments, the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40 inhibitor is resistant to said immunoglobulin degrading enzyme.

[092] In some embodiments, the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, HNSA-5487 .

[093] In some embodiments, wherein the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

[094] In another aspect, provided herein is a method for increasing or maintaining the level of a transgene expression in a subject in need thereof, said method comprising administering to the subject an effective amount of a CD40 inhibitor.

[095] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[096] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[097] In some embodiments, the transgene is delivered to the subject via an immunogenic delivery vehicle.

[098] In some embodiments, the level of transgene expression is increased or maintained by inhibiting an immune response to the immunogenic delivery vehicle and/or by inhibiting an immune response to the transgene product(s) (e.g., a polypeptide or polynucleotide encoded by the transgene).

[099] In some embodiments, the level of transgene expression is increased or maintained by inhibiting antibody responses to the transgene product(s) (e.g., a polypeptide or polynucleotide encoded by the transgene).

[0100] In certain embodiments, the CD40 inhibitor is administered before the administration of the immunogenic delivery vehicle to the subject.

[0101] In certain embodiments, the CD40 inhibitor is administered simultaneously with the administration of the immunogenic delivery vehicle to the subject.

[0102] In certain embodiments, the CD40 inhibitor is administered after the administration of the immunogenic delivery vehicle to the subject.

[0103] In certain embodiments, the immunogenic delivery vehicle is administered to the subject two or more times and the CD40 inhibitor is administered before and/or between each of the administrations of the immunogenic delivery vehicle.

[0104] In some embodiments, the subject has a preexisting immune response to the immunogenic delivery vehicle and/or to the transgene product(s).

[0105] In some embodiments, the method further comprises administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

[0106] In some embodiments, the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

[0107] In some embodiments, the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

[0108] In some embodiments, the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

[0109] In some embodiments, the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

[0110] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0111] In some embodiments, the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0112] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0113] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0114] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0115] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0116] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0117] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0118] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0119] In some embodiments, the method further comprises administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

[0120] In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

[0121] In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[0122] In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[0123] In some embodiments, the B cell depleting agent is an agent that binds to a B cell surface molecule.

[0124] In some embodiments, the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

[0125] In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

[0126] In some embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

[0127] In some embodiments, the multispecific anti-CD20 antibody or functional fragment thereof is anti-CD20xCD3 bispecific antibody or functional fragment thereof.

[0128] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0129] In some embodiments, the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0130] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable

region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0131] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0132] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[0133] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0134] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0135] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0136] In some embodiments, the B cell depleting agent is an agent targeting a B cell survival factor.

[0137] In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

[0138] In some embodiments, the immunoglobulin depleting agent is capable of accelerating IgG clearance.

[0139] In some embodiments, the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

[0140] In some embodiments, the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

[0141] In some embodiments, the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

[0142] In some embodiments, the plasma cell depleting agent is administered simultaneously with the immunogenic delivery vehicle, prior to the immunogenic delivery vehicle, or prior to and after the immunogenic delivery vehicle,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogenic delivery vehicle and the plasma cell depleting agent is administered if the immunogenic delivery vehicle and/or transgene product(s) are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogenic delivery vehicle.

[0143] In some embodiments, the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent is administered prior to the CD40 inhibitor.

[0144] In some embodiments, the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent and the CD40 inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogenic delivery vehicle and/or to the transgene product(s) when the plasma cell depleting agent and the CD40 inhibitor are administered.

[0145] In some embodiments,

(I) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of a first dose of the immunogenic delivery vehicle, the CD40 inhibitor is administered prior to the first dose of the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene product(s) from the first dose of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the first dose of the immunogenic delivery vehicle but prior to administration of a second dose of the immunogenic delivery vehicle; or

(II) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of the immunogenic delivery vehicle, the CD40 inhibitor is administered prior to the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene product(s) from the administration of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the immunogenic delivery vehicle but prior to administration of a second immunogenic delivery vehicle.

[0146] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0147] In one embodiment, the immunogenic delivery vehicle is a viral vector.

[0148] In a further aspect, provided herein is a method for increasing effectiveness of administration of a subsequently administered viral vector following administration of an originally administered viral vector in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor, wherein the subsequently administered viral vector is of the same or similar viral origin as the originally administered viral vector.

[0149] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[0150] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[0151] In some embodiments, the subsequently administered viral vector is administered via the same administration route as the originally administered viral vector.

[0152] In some embodiments, the subsequently administered viral vector is administered via a different administration route from the originally administered viral vector

[0153] In certain embodiments, the CD40 inhibitor is administered before the administration of the originally administered viral vector to the subject.

[0154] In certain embodiments, the CD40 inhibitor is administered simultaneously with the administration of the originally administered viral vector and/or subsequently administered viral vector to the subject.

[0155] In certain embodiments, the CD40 inhibitor is administered after the administration of the originally administered viral vector but before administering the subsequently administered viral vector to the subject.

[0156] In certain embodiments, the CD40 inhibitor is administered after the administration of the subsequently administered viral vector to the subject.

[0157] In certain embodiments, the CD40 inhibitor is administered before and/or between each of the subsequently administered administrations of the viral vectors to the subject.

[0158] In some embodiments, the subject has a preexisting immune response to the viral vectors.

[0159] In some embodiments, the method further comprises administering to the subject a plasma cell depleting agent when the subject has preexisting immunity against the viral vectors.

[0160] In some embodiments, the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

[0161] In some embodiments, the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

[0162] In some embodiments, the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

[0163] In some embodiments, the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

[0164] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0165] In some embodiments, the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0166] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0167] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0168] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0169] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0170] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0171] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0172] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0173] In some embodiments, the method further comprises administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent when the subject has preexisting immunity against the viral vectors.

[0174] In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

[0175] In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[0176] In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[0177] In some embodiments, the B cell depleting agent is an agent that binds to a B cell surface molecule.

[0178] In some embodiments, the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

[0179] In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

[0180] In some embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

[0181] In some embodiments, the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

[0182] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region

(HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0183] In some embodiments, the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0184] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0185] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0186] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[0187] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0188] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0189] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0190] In some embodiments, the B cell depleting agent is an agent targeting a B cell survival factor.

[0191] In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

[0192] In some embodiments, the immunoglobulin depleting agent is capable of accelerating IgG clearance.

[0193] In some embodiments, the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

[0194] In some embodiments, the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

[0195] In some embodiments, the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

[0196] In some embodiments, the plasma cell depleting agent is administered simultaneously with the viral vectors, prior to the viral vectors, or prior to and after the viral vectors,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the viral vectors and the plasma cell depleting agent is administered if the viral vectors are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior the viral vectors.

[0197] In some embodiments, the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent is administered prior to the CD40 inhibitor.

[0198] In some embodiments, the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent and the CD40 inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the viral vectors when the plasma cell depleting agent and the CD40 inhibitor are administered.

[0199] In some embodiments,

(I) the subject does not have preexisting immunity against the viral vectors before administration of a first dose of the viral vectors, the CD40 inhibitor is administered prior to the first dose of the viral vectors, the subject develops immunity against the viral vectors from the first dose of the viral vectors, and the plasma cell depleting agent is administered after the first dose of the viral vectors but prior to a second dose of the viral vectors; or

(II) the subject does not have preexisting immunity against the viral vectors before administration of the viral vectors, the CD40 inhibitor is administered prior to the viral vectors, the subject develops immunity against the viral vectors from the administration of the viral vectors, and the plasma cell depleting agent is administered after the viral vectors but prior to administration of second viral vectors.

[0200] In some embodiments, the viral vectors are derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

[0201] In certain embodiments, the viral vectors are derived from AAV.

[0202] In one embodiment, the subsequently administered AAV vector has a capsid derived from the same AAV serotype as the originally administered AAV vector.

[0203] In one embodiment, the retrovirus is a lentivirus.

[0204] In certain embodiments, the viral vectors are derived from an oncolytic virus.

[0205] In certain embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0206] In some embodiments, the CD40 inhibitor

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

[0207] In some embodiments, the CD40 inhibitor inhibits CD40L-induced activation. In some embodiments, the CD40 inhibitor inhibits CD40L-induced activation and does not significantly agonize CD40 in the absence of CD40L.

[0208] In some embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

[0209] In certain embodiments, the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof.

[0210] In certain embodiments, the anti-CD40 antibody is an anti-CD40 monospecific antibody or a functional fragment thereof.

[0211] In one embodiment, the anti-CD40 antibody is an anti-CD40 bivalent antibody or a functional fragment thereof.

[0212] In one embodiment, the anti-CD40 antibody is an anti-CD40 biparatopic antibody or a functional fragment thereof.

[0213] In some embodiments, the anti-CD40 antibody is a multispecific antibody or a functional fragment thereof.

[0214] In some embodiments, the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

[0215] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain variable region (HCVR) comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188, or a variant thereof; and/or

b) a light chain variable region (LCVR) comprising the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence of SEQ ID NO: 10, 61, 71, 81, 90, 100, 106, 113, 121, 130, 145, 148, 150, 154, 167, 177, 182 or 190, or a variant thereof.

[0216] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR

comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

[0217] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0218] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

d) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 58, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof;

e) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 68, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

f) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 78, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

g) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 87, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 92, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93, or a variant thereof;

h) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

i) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 110, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof;

j) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a

variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

k) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 127, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof;

l) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 153, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

m) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 164, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof;

n) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof; and/or

o) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof.

[0219] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and/or

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0220] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

[0221] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0222] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

d) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 65, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

e) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 75, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

f) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 84, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

g) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 94, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 95, or a variant thereof;

h) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 104, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

i) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 107, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 108, or a variant thereof;

j) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 117, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 118, or a variant thereof;

k) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 123, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

l) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

m) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 134, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 135, or a variant thereof;

n) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 151, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

o) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 155, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

p) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 157, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

q) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 158, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

r) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 159, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

s) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 160, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

t)a heavy chain that comprises the amino acid sequence of SEQ ID NO: 161, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

u) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 162, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

v) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 171, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

w) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 173, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

x) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 174, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

y) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 175, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

z) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 187, or a variant thereof;

aa) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 191, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof; and/or

bb) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof.

[0223] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and/or

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0224] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

[0225] In certain embodiments, the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or variant thereof; and

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or variant thereof.

[0226] In certain embodiments, the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, or a variant thereof, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0227] In certain embodiments, the D1 domain comprises:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0228] In certain embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid

sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0229] In certain embodiments, the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

[0230] In certain embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0231] In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof.

[0232] In certain embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0233] In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

[0234] In certain embodiments, the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0235] In certain embodiments, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0236] In certain embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

[0237] In certain embodiments, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0238] In certain embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

[0239] In certain embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0240] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0241] In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0242] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0243] In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0244] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D1 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32. In certain embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0245] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D2 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In

certain embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0246] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0247] In certain embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0248] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises a human IgG heavy chain constant region.

[0249] In some embodiments, the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0250] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0251] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0252] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that reduces binding to an Fc receptor (e.g., one or more modifications in a hinge region and/or CH region).

[0253] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D1 domain comprising:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0254] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D2 domain comprising:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0255] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0256] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino

acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0257] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0258] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0259] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0260] In a further aspect, provided herein is a composition comprising an immunogen and a CD40 inhibitor and optionally further comprising a pharmaceutically acceptable carrier and/or excipient.

[0261] In some embodiments, the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[0262] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[0263] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[0264] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0265] In some embodiments, the immunogenic delivery vehicle is a viral vector.

[0266] In some embodiments, the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

[0267] In some embodiments, the viral vector is derived from AAV.

[0268] In some embodiments, the retrovirus is a lentivirus.

[0269] In some embodiments, the viral vector is derived from an oncolytic virus.

[0270] In certain embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0271] In certain embodiments, the CD40 inhibitor:

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

[0272] In some embodiments, the CD40 inhibitor inhibits CD40L-induced activation. In some embodiments, the CD40 inhibitor inhibits CD40L-induced activation and does not significantly agonize CD40 in the absence of CD40L.

[0273] In certain embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

[0274] In certain embodiments, the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof.

[0275] In certain embodiments, the anti-CD40 antibody is an anti-CD40 monospecific antibody or a functional fragment thereof.

[0276] In certain embodiments, the anti-CD40 antibody is an anti-CD40 bivalent antibody or a functional fragment thereof.

[0277] In certain embodiments, the anti-CD40 antibody is an anti-CD40 biparatopic antibody or a functional fragment thereof.

[0278] In certain embodiments, the anti-CD40 antibody is a multispecific antibody or a functional fragment thereof.

[0279] In certain embodiments, the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

[0280] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain variable region (HCVR) comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188, or a variant thereof; and/or

b) a light chain variable region (LCVR) comprising the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence of SEQ ID NO: 10, 61, 71, 81, 90, 100, 106, 113, 121, 130, 145, 148, 150, 154, 167, 177, 182 or 190, or a variant thereof.

[0281] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR

comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

[0282] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0283] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

d) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 58, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof;

e) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 68, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

f)an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 78, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

g) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 87, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 92, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93, or a variant thereof;

h) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

i) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 110, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof;

j) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

k) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 127, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128,

or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof;

l) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 153, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

m) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 164, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof;

n) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof; and/or

o) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof.

[0284] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and/or

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0285] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

[0286] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0287] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

d) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 65, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

e) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 75, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

f)a heavy chain that comprises the amino acid sequence of SEQ ID NO: 84, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

g) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 94, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 95, or a variant thereof;

h) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 104, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

i) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 107, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 108, or a variant thereof;

j) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 117, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 118, or a variant thereof;

k) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 123, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

l) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

m) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 134, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 135, or a variant thereof;

n) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 151, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

o) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 155, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

p) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 157, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

q) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 158, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

r) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 159, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

s) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 160, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

t)a heavy chain that comprises the amino acid sequence of SEQ ID NO: 161, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

u) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 162, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

v) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 171, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

w) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 173, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

x) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 174, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

y) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 175, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

z) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 187, or a variant thereof;

aa) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 191, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof; and/or

bb) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof.

[0288] In some embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and/or

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0289] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

[0290] In some embodiments, the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof.

[0291] In some embodiments, the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, or a variant thereof, the LCDR2 comprises the amino

acid sequence of SEQ ID NO: 14, or a variant thereof, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0292] In some embodiments, the D1 domain comprises:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26 or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36 or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0293] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0294] In one embodiment, the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

[0295] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid

sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0296] In one embodiment, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof.

[0297] In one embodiment, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0298] In one embodiment, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

[0299] In one embodiment, the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0300] In some embodiments, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0301] In one embodiment, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

[0302] In one embodiment, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0303] In one embodiment, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

[0304] In one embodiment, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0305] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0306] In some embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0307] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0308] In some embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0309] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D1 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32. In some embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0310] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D2 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2. In some embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0311] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of

SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0312] In some embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0313] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a human IgG heavy chain constant region.

[0314] In certain embodiments, the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0315] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0316] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0317] In certain embodiments, the human IgG heavy chain constant region comprises one or more modifications that reduces binding to an Fc receptor (e.g., one or more modifications in a hinge region and/or CH region).

[0318] In some embodiments, the D1 domain comprises:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0319] In some embodiments, the D2 domain comprises:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0320] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0321] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0322] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0323] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0324] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0325] In another aspect, provided herein is a kit comprising (i) an immunogen, (ii) a CD40 inhibitor, and (iii) optionally, instructions for use.

[0326] In some embodiments, the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[0327] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[0328] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[0329] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0330] In some embodiments, the immunogenic delivery vehicle is a viral vector.

[0331] In some embodiments, the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

[0332] In certain embodiments, the viral vector is derived from AAV.

[0333] In certain embodiments, the retrovirus is a lentivirus.

[0334] In certain embodiments, the viral vector is derived from an oncolytic virus.

[0335] In certain embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0336] In some embodiments, the CD40 inhibitor:

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

[0337] In some embodiments, the CD40 inhibitor inhibits CD40L-induced activation. In some embodiments, the CD40 inhibitor inhibits CD40L-induced activation and does not significantly agonize CD40 in the absence of CD40L.

[0338] In some embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

[0339] In some embodiments, the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof.

[0340] In some embodiments, the anti-CD40 antibody is a monospecific anti-CD40 antibody or the functional fragment thereof.

[0341] In some embodiments, the anti-CD40 antibody is an anti-CD40 bivalent antibody or a functional fragment thereof.

[0342] In some embodiments, the anti-CD40 antibody is an anti-CD40 biparatopic antibody or a functional fragment thereof.

[0343] In some embodiments, the anti-CD40 antibody is a multispecific anti-CD40 antibody or the functional fragment thereof.

[0344] In some embodiments, the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

[0345] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain variable region (HCVR) comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188, or a variant thereof; and/or

b) a light chain variable region (LCVR) comprising the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence of SEQ ID NO: 10, 61, 71, 81, 90, 100, 106, 113, 121, 130, 145, 148, 150, 154, 167, 177, 182 or 190, or a variant thereof.

[0346] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR

comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

[0347] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising

the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0348] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

d) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 58, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59,

or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof;

e) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 68, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

f)an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 78, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

g) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 87, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 92, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93, or a variant thereof;

h) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

i) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 110, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof;

j) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

k) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 127, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof;

l) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 153, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

m) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 164, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof;

n) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof; and/or

o) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof.

[0349] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and/or

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0350] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t)an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

[0351] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0352] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

d) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 65, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

e) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 75, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

f) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 84, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

g) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 94, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 95, or a variant thereof;

h) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 104, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

i) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 107, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 108, or a variant thereof;

j) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 117, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 118, or a variant thereof;

k) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 123, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

l) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

m) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 134, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 135, or a variant thereof;

n) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 151, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

o) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 155, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

p) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 157, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

q) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 158, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

r) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 159, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

s) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 160, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

t) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 161, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

u) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 162, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

v) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 171, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

w) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 173, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

x) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 174, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

y) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 175, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

z) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 187, or a variant thereof;

aa) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 191, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof; and/or

bb) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof.

[0353] In certain embodiments, the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and/or

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0354] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

[0355] In certain embodiments, the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof.

[0356] In certain embodiments, the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, or a variant thereof, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0357] In certain embodiments, the D1 domain comprises:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16 or a variant thereof; or

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0358] In certain embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0359] In one embodiment, the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

[0360] In certain embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0361] In one embodiment, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof.

[0362] In one embodiment, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0363] In one embodiment, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

[0364] In one embodiment, the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0365] In certain embodiments, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12 or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0366] In one embodiment, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

[0367] In one embodiment, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0368] In one embodiment, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

[0369] In one embodiment, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0370] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO:

38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0371] In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0372] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

[0373] In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

[0374] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D1 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In

certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32. In certain embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0375] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D2 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In certain embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0376] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0377] In certain embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0378] In some embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a human IgG heavy chain constant region.

[0379] In some embodiments, the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0380] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0381] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0382] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that reduces binding to an Fc receptor (e.g., one or more modifications in a hinge region and/or CH region).

[0383] In certain embodiments, the D1 domain comprises:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0384] In certain embodiments, the D2 domain comprises:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0385] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino

acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0386] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0387] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0388] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0389] In certain embodiments, the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

[0390] In a further aspect, provided herein is a method for inhibiting an immune response to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

[0391] In another aspect, provided herein is a method for inhibiting generation of neutralizing antibodies to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

[0392] In another aspect, provided herein is a method for preventing and/or suppressing an immunogen-specific T cell response in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

[0393] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises suppression of numbers and/or frequencies of the immunogen-specific T cells.

[0394] In some embodiments, the immunogen-specific T cells comprise follicular T helper cells (TFH) and/or CD4+ T cells.

[0395] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or a tissue in the subject in response to the immunogen.

[0396] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle, and the prevention and/or suppression of the immunogen-specific T cell response comprises increasing or maintaining the level of transgene expression in the subject.

[0397] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or tissue in the subject in response to transgene expression in the organ and/or a tissue.

[0398] In some embodiments, the tissue is muscle.

[0399] In some embodiments, the organ is liver.

[0400] In a further aspect, provided herein is a method for increasing effectiveness of re-administration of an immunogen to a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

[0401] In some embodiments, the immunogen re-administration occurs via the same administration route as its prior administration.

[0402] In some embodiments, the immunogen re-administration occurs via a different administration route than its prior administration.

[0403] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[0404] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[0405] In certain embodiments, the CD40L inhibitor is administered before the administration of the immunogen to the subject.

[0406] In certain embodiments, the CD40L inhibitor is administered simultaneously with the administration of the immunogen to the subject.

[0407] In certain embodiments, the CD40L inhibitor is administered after the administration of the immunogen to the subject.

[0408] In certain embodiments, the immunogen is administered to the subject two or more times and the CD40L inhibitor is administered before and/or between each of the administrations of the immunogen.

[0409] In some embodiments, the subject has a preexisting immune response to the immunogen.

[0410] In some embodiments, the method further comprises administering to the subject an immunoglobulin depleting agent.

[0411] In some embodiments, the immunoglobulin depleting agent is administered before the administration of the CD40L inhibitor to the subject, and the CD40L inhibitor is administered before the administration of the immunogen to the subject.

[0412] In some embodiments, the CD40L inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, and the immunoglobulin depleting agent is administered before the administration of the immunogen to the subject.

[0413] In some embodiments, the CD40L inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject has preexisting immunity against the immunogen.

[0414] In some embodiments, the CD40L inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject does not have preexisting immunity against the immunogen.

[0415] In some embodiments, the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40L inhibitor is resistant to said immunoglobulin degrading enzyme.

[0416] In some embodiments, the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, and HNSA-5487.

[0417] In some embodiments, the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

[0418] In some embodiments, the method further comprises administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogen.

[0419] In some embodiments, the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

[0420] In some embodiments, the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

[0421] In some embodiments, the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

[0422] In some embodiments, the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

[0423] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0424] In some embodiments, the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0425] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0426] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0427] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0428] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0429] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0430] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0431] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0432] In some embodiments, the method further comprises administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogen.

[0433] In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

[0434] In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[0435] In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[0436] In some embodiments, the B cell depleting agent is an agent that binds to a B cell surface molecule.

[0437] In some embodiments, the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

[0438] In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

[0439] In some embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

[0440] In some embodiments, the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

[0441] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0442] In some embodiments, the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO:

1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0443] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0444] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0445] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[0446] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0447] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0448] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0449] In some embodiments, the B cell depleting agent is an agent targeting a B cell survival factor.

[0450] In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

[0451] In some embodiments, the immunoglobulin depleting agent is capable of accelerating IgG clearance.

[0452] In some embodiments, the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

[0453] In some embodiments, the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

[0454] In some embodiments, the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

[0455] In some embodiments, the plasma cell depleting agent is administered simultaneously with the immunogen, prior to the immunogen, or prior to and after the immunogen,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogen and the plasma cell depleting agent is administered if the immunogen is still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogen.

[0456] In some embodiments, the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent is administered prior to the CD40L inhibitor.

[0457] In some embodiments, the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent and the CD40L inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogen when the plasma cell depleting agent and the CD40L inhibitor are administered.

[0458] In some embodiments,

(I) the subject does not have preexisting immunity against the immunogen before administration of a first dose of the immunogen, the CD40L inhibitor is administered prior to the first dose of the immunogen, the subject develops immunity against the immunogen from the first dose of the immunogen, and the plasma cell depleting agent is administered after the first dose of the immunogen but prior to a second dose of the immunogen; or

(II) the subject does not have preexisting immunity against the immunogen before administration of the immunogen, the CD40L inhibitor is administered prior to the

immunogen, the subject develops immunity against the immunogen from the administration of the immunogen, and the plasma cell depleting agent is administered after the immunogen but prior to administration of a second immunogen.

[0459] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[0460] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[0461] In one embodiment, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[0462] In some embodiments, the immunogen is an immunoglobulin depleting agent.

[0463] In some embodiments, the immunoglobulin depleting agent is administered before the administration of the CD40L inhibitor to the subject at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

[0464] In some embodiments, the immunoglobulin depleting agent is administered before the administration of the CD40L inhibitor to the subject at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

[0465] In some embodiments, the CD40L inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

[0466] In some embodiments, the CD40L inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

[0467] In some embodiments, the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40L inhibitor is resistant to said immunoglobulin degrading enzyme.

[0468] In some embodiments, the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, HNSA-5487 .

[0469] In some embodiments, the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

[0470] In another aspect, provided herein is a method for increasing or maintaining the level of a transgene expression in a subject in need thereof, said method comprising administering to the subject an effective amount of a CD40L inhibitor.

[0471] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[0472] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[0473] In some embodiments, the transgene is delivered to the subject via an immunogenic delivery vehicle.

[0474] In some embodiments, the level of transgene expression is increased or maintained by inhibiting an immune response to the immunogenic delivery vehicle and/or by inhibiting an immune response to the transgene product(s) (e.g., a polypeptide or polynucleotide encoded by the transgene).

[0475] In some embodiments, the level of transgene expression is increased or maintained by inhibiting antibody responses to the transgene product(s) (e.g., a polypeptide or polynucleotide encoded by the transgene).

[0476] In certain embodiments, the CD40L inhibitor is administered before the administration of the immunogenic delivery vehicle to the subject.

[0477] In certain embodiments, the CD40L inhibitor is administered simultaneously with the administration of the immunogenic delivery vehicle to the subject.

[0478] In certain embodiments, the CD40L inhibitor is administered after the administration of the immunogenic delivery vehicle to the subject.

[0479] In some embodiments, the immunogenic delivery vehicle is administered to the subject two or more times and the CD40L inhibitor is administered before and/or between each of the administrations of the immunogenic delivery vehicle.

[0480] In some embodiments, the subject has a preexisting immune response to the immunogenic delivery vehicle and/or to the transgene product(s).

[0481] In some embodiments, the method further comprises administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

[0482] In some embodiments, the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

[0483] In some embodiments, the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

[0484] In some embodiments, the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

[0485] In some embodiments, the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

[0486] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0487] In some embodiments, the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0488] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0489] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0490] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0491] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0492] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0493] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0494] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0495] In some embodiments, the method further comprises administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

[0496] In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

[0497] In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[0498] In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[0499] In some embodiments, the B cell depleting agent is an agent that binds to a B cell surface molecule.

[0500] In some embodiments, the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

[0501] In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

[0502] In some embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

[0503] In some embodiments, the multispecific anti-CD20 antibody or functional fragment thereof is anti-CD20xCD3 bispecific antibody or functional fragment thereof.

[0504] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0505] In some embodiments, the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0506] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable

region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0507] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0508] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[0509] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0510] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0511] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0512] In some embodiments, the B cell depleting agent is an agent targeting a B cell survival factor.

[0513] In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

[0514] In some embodiments, the immunoglobulin depleting agent is capable of accelerating IgG clearance.

[0515] In some embodiments, the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

[0516] In some embodiments, the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

[0517] In some embodiments, the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

[0518] In some embodiments, the plasma cell depleting agent is administered simultaneously with the immunogenic delivery vehicle, prior to the immunogenic delivery vehicle, or prior to and after the immunogenic delivery vehicle,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogenic delivery vehicle and the plasma cell depleting agent is administered if the immunogenic delivery vehicle and/or transgene product(s) are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogenic delivery vehicle.

[0519] In some embodiments, the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent is administered prior to the CD40L inhibitor.

[0520] In some embodiments, the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent and the CD40L inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogenic delivery vehicle and/or to the transgene product(s) when the plasma cell depleting agent and the CD40L inhibitor are administered.

[0521] In some embodiments,

(I) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of a first dose of the immunogenic delivery vehicle, the CD40L inhibitor is administered prior to the first dose of the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene product(s) from the first dose of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the first dose of the immunogenic delivery vehicle but prior to administration of a second dose of the immunogenic delivery vehicle; or

(II) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of the immunogenic delivery vehicle, the CD40L inhibitor is administered prior to the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene product(s) from the administration of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the immunogenic delivery vehicle but prior to administration of a second immunogenic delivery vehicle.

[0522] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0523] In one embodiment, the immunogenic delivery vehicle is a viral vector.

[0524] In a further aspect, provided herein is a method for increasing effectiveness of administration of a subsequently administered viral vector following administration of an originally administered viral vector in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor, wherein the subsequently administered viral vector is of the same or similar viral origin as the originally administered viral vector.

[0525] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[0526] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[0527] In some embodiments, the subsequently administered viral vector is administered via the same administration route as the originally administered viral vector.

[0528] In some embodiments, the subsequently administered viral vector is administered via a different administration route from the originally administered viral vector.

[0529] In certain embodiments, the CD40L inhibitor is administered before the administration of the originally administered viral vector to the subject.

[0530] In certain embodiments, the CD40L inhibitor is administered simultaneously with the administration of the originally administered viral vector and/or subsequently administered viral vector to the subject.

[0531] In certain embodiments, the CD40L inhibitor is administered after the administration of the originally administered viral vector but before administering the subsequently administered viral vector to the subject.

[0532] In certain embodiments, the CD40L inhibitor is administered after the administration of the subsequently administered viral vector to the subject.

[0533] In certain embodiments, the CD40L inhibitor is administered before and/or between each of the subsequently administered administrations of the viral vectors to the subject.

[0534] In some embodiments, the subject has a preexisting immune response to the viral vectors.

[0535] In some embodiments, the method further comprises administering to the subject a plasma cell depleting agent when the subject has preexisting immunity against the viral vectors.

[0536] In some embodiments, the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

[0537] In some embodiments, the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

[0538] In some embodiments, the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

[0539] In some embodiments, the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

[0540] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0541] In some embodiments, the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0542] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

[0543] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

[0544] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0545] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[0546] In some embodiments, the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0547] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0548] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0549] In some embodiments, the method further comprises administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent when the subject has preexisting immunity against the viral vectors.

[0550] In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

[0551] In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[0552] In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[0553] In some embodiments, the B cell depleting agent is an agent that binds to a B cell surface molecule.

[0554] In some embodiments, the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

[0555] In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

[0556] In some embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

[0557] In some embodiments, the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

[0558] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region

(HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0559] In some embodiments, the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0560] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

[0561] In some embodiments, the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

[0562] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[0563] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

[0564] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

[0565] In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

[0566] In some embodiments, the B cell depleting agent is an agent targeting a B cell survival factor.

[0567] In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

[0568] In some embodiments, the immunoglobulin depleting agent is capable of accelerating IgG clearance.

[0569] In some embodiments, the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

[0570] In some embodiments, the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

[0571] In some embodiments, the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

[0572] In some embodiments, the plasma cell depleting agent is administered simultaneously with the viral vectors, prior to the viral vectors, or prior to and after the viral vectors,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the viral vectors and the plasma cell depleting agent is administered if the viral vectors are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior the viral vectors.

[0573] In some embodiments, the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent is administered prior to the CD40L inhibitor.

[0574] In some embodiments, the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent and the CD40L inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the viral vectors when the plasma cell depleting agent and the CD40L inhibitor are administered.

[0575] In some embodiments,

(I) the subject does not have preexisting immunity against the viral vectors before administration of a first dose of the viral vectors, the CD40L inhibitor is administered prior to the first dose of the viral vectors, the subject develops immunity against the viral vectors from the first dose of the viral vectors, and the plasma cell depleting agent is administered after the first dose of the viral vectors but prior to a second dose of the viral vectors; or

(II) the subject does not have preexisting immunity against the viral vectors before administration of the viral vectors, the CD40L inhibitor is administered prior to the viral vectors, the subject develops immunity against the viral vectors from the administration of the viral vectors, and the plasma cell depleting agent is administered after the viral vectors but prior to administration of second viral vectors.

[0576] In some embodiments, the viral vectors are derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

[0577] In some embodiments, the viral vectors are derived from AAV.

[0578] In one embodiment, the subsequently administered AAV vector has a capsid derived from the same AAV serotype as the originally administered AAV vector.

[0579] In some embodiments, the retrovirus is a lentivirus.

[0580] In some embodiments, the viral vectors are derived from an oncolytic virus.

[0581] In certain embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0582] In some embodiments, the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof, a CD40L binding protein or a functional fragment thereof, or an oligonucleotide or a functional fragment thereof.

[0583] In some embodiments, the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof.

[0584] In some embodiments, the anti-CD40L antibody is an antagonistic anti-CD40L antibody or a functional fragment thereof.

[0585] In some embodiments, the anti-CD40L antibody is an anti-CD40L monospecific antibody or a functional fragment thereof.

[0586] In some embodiments, the anti-CD40L antibody is a multispecific antibody or a functional fragment thereof.

[0587] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

[0588] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 194, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof.

[0589] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

[0590] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

a heavy chain that comprises the amino acid sequence of SEQ ID NO: 201, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 202, or a variant thereof.

[0591] In some embodiments, the CD40L inhibitor is a CD40L-binding protein or a functional fragment thereof.

[0592] In some embodiments, the CD40L-binding protein or the functional fragment thereof comprises the amino acid sequence of SEQ ID NO: 203, or a variant thereof.

[0593] In one embodiment, the CD40L-binding protein consists of the amino acid sequence of SEQ ID NO: 203.

[0594] In another aspect, provided herein is a composition comprising an immunogen and a CD40L inhibitor and optionally further comprising a pharmaceutically acceptable carrier and/or excipient.

[0595] In some embodiments, the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[0596] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[0597] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[0598] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0599] In some embodiments, the immunogenic delivery vehicle is a viral vector.

[0600] In some embodiments, the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, a retrovirus.

[0601] In one embodiment, the viral vector is derived from AAV.

[0602] In one embodiment, the retrovirus is a lentivirus.

[0603] In some embodiments, the viral vector is derived from an oncolytic virus.

[0604] In certain embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0605] In some embodiments, the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof, a CD40L binding protein or a functional fragment thereof, or an oligonucleotide or a functional fragment thereof.

[0606] In some embodiments, the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof.

[0607] In some embodiments, the anti-CD40L antibody is an antagonistic anti-CD40L antibody or a functional fragment thereof.

[0608] In some embodiments, the anti-CD40L antibody is an anti-CD40L monospecific antibody or a functional fragment thereof.

[0609] In some embodiments, the anti-CD40L antibody is a multispecific antibody or a functional fragment thereof.

[0610] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR comprising

the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

[0611] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 194, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof.

[0612] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

[0613] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

a heavy chain that comprises the amino acid sequence of SEQ ID NO: 201, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 202, or a variant thereof.

[0614] In some embodiments, the CD40L inhibitor is a CD40L-binding protein or a functional fragment thereof.

[0615] In some embodiments, the CD40L-binding protein or the functional fragment thereof comprises the amino acid sequence of SEQ ID NO: 203, or a variant thereof.

[0616] In some embodiments, the CD40L-binding protein consists of the amino acid sequence of SEQ ID NO: 203.

[0617] In a further aspect, provided herein is a kit comprising (i) an immunogen, (ii) a CD40L inhibitor, and (iii) optionally, instructions for use.

[0618] In some embodiments, the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[0619] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[0620] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[0621] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0622] In some embodiments, the immunogenic delivery vehicle is a viral vector.

[0623] In some embodiments, the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

[0624] In one embodiment, the viral vector is derived from AAV.

[0625] In one embodiment, the retrovirus is a lentivirus.

[0626] In certain embodiments, the viral vector is derived from an oncolytic virus.

[0627] In certain embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0628] In some embodiments, the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof, a CD40L binding protein or a functional fragment thereof, or an oligonucleotide or a functional fragment thereof.

[0629] In some embodiments, theCD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof.

[0630] In some embodiments, the anti-CD40L antibody is an antagonistic anti-CD40L antibody or a functional fragment thereof.

[0631] In some embodiments, the anti-CD40L antibody is an anti-CD40L monospecific antibody or a functional fragment thereof.

[0632] In some embodiments, the anti-CD40L antibody is a multispecific antibody or a functional fragment thereof.

[0633] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

[0634] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 194, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof.

[0635] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

[0636] In certain embodiments, the anti-CD40L antibody or the functional fragment thereof comprises:

a heavy chain that comprises the amino acid sequence of SEQ ID NO: 201, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 202, or a variant thereof.

[0637] In some embodiments, the CD40L inhibitor is a CD40L-binding protein or a functional fragment thereof.

[0638] In one embodiment, the CD40L-binding protein or the functional fragment thereof comprises the amino acid sequence of SEQ ID NO: 203, or a variant thereof.

[0639] In one embodiment, the CD40L-binding protein consists of the amino acid sequence of SEQ ID NO: 203.

[0640] These and other aspects described herein will be apparent to those of ordinary skill in the art in the following description, claims, and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0641] **Figures 1A-1C** show the effect of anti-CD40xCD40 bispecific antibodies on IL6 production in the presence of constant CD40L in human B cells from three different donors.

Figures 1D-1E show the effect of CD40xCD40 bispecific antibodies on IL6 production in the presence of constant CD40L in human B cells from two different donors.

[0642] **Figures 2A-2C** show the effect of anti-CD40xCD40 bispecific antibodies on IL10 production in the presence of constant CD40L in human B cells from three different donors. **Figures 2D-2E** show the effect of CD40xCD40 bispecific antibodies on IL10 production in the presence of constant CD40L in human B cells from two different donors.

[0643] **Figures 3A-3C** show the effect of anti-CD40xCD40 bispecific antibodies on TNFα production in the presence of constant CD40L in human B cells from three different donors. **Figures 3D-3E** show the effect of CD40xCD40 bispecific antibodies on TNFα production in the presence of constant CD40L in human B cells from two different donors. **Figures 3F-3G** show analysis of agonist activity of CD40xCD40 bispecific antibodies as measured by IL6 production in human B cells from two different donors.

[0644] **Figures 4A-4B** show the effect of anti-CD40xCD40 bispecific antibodies on IL-12/IL-23p40 production in the presence of constant CD40L from human monocyte derived dendritic cells from two different donors.

[0645] **Figures 5A-5B** show analysis of agonist activity of anti-CD40xCD40 bispecific antibodies as measured by IL6 production in human B cells from two different donors.

[0646] **Figures 6A-6B** show analysis of agonist activity of anti-CD40xCD40 bispecific antibodies as measured by IL10 production in human B cells from two different donors

[0647] **Figure 7** shows an experiment timeline using a NP-KLH immunization model as disclosed in Example 9.

[0648] **Figure 8A** shows the effect of anti-CD40xCD40 bispecific antibodies on the frequency of NP positive germinal center B cells. * $p<0.05$. **Figure 8B** shows the effect of anti-CD40xCD40 bispecific antibodies on the frequency of NP IgG1 titers in mouse serum. * $p<0.05$; ** $p<0.005$.

[0649] **Figure 9A** shows the effect of CD40xCD40 bispecific antibodies on the frequency of NP positive germinal center B cells. **Figure 9B** shows the effect of CD40xCD40 bispecific antibodies on the frequency of NP IgG1 titers in mouse serum.

[0650] **Figure 10** shows an experiment timeline using a mouse EAE model as disclosed in Example 10.

[0651] **Figure 11A** shows mean EAE symptom scores for REGN16431- or REGN16432-treated mice. **Figure 11B** shows mean EAE symptom scores for REGN16334- or REGN16335-treated mice. **Figure 11C** shows percent of initial body weight in REGN16431- or REGN16432-treated mice. **Figure 11D** shows percent of initial body weight in REGN16334- or REGN16335-treated mice.

[0652] **Figure 12A** shows mean EAE symptom scores for CD40xCD40 bispecific antibody-treated mice. **Figure 12B** shows percent of initial body weight in CD40xCD40 bispecific antibody-treated mice.

[0653] **Figure 13** shows an experiment timeline for the study described in Example 11.

[0654] **Figure 14** shows the effect of antibody-mediated CD40L blockade on the development of anti-AAV IgG titers following treatment with a AAV8 vector.

[0655] **Figures 15A-15C** show the effect of antibody-mediated CD40L blockade on transduction by a second AAV8 vector.

[0656] **Figure 16** shows an experiment timeline for the study described in Examples 12, 13, and 16.

[0657] **Figures 17A-17B** show the effect of antagonistic anti-CD40 antibodies on the development of anti-AAV IgG and IgM titers following treatment with an AAV8 vector.

[0658] **Figures 18A-18C** show the effect of antagonistic anti-CD40 antibodies on transduction by a second AAV8 vector.

[0659] **Figure 19** shows an experiment timeline for the study described in Examples 14 and 15.

[0660] **Figures 20A-20D** show the effect of antagonistic anti-CD40 antibodies on steady-state polyclonal and AAV-specific germinal center B cell responses.

[0661] **Figures 21A-21E** show the effect of antagonistic anti-CD40 antibodies on follicular T helper cell (TFH) responses and AAV-specific T cell responses.

[0662] **Figure 22** shows the effect of antagonistic anti-CD40 antibodies on the development of anti-transgene IgG following treatment with an AAV8 vector.

[0663] **Figure 23** shows a cryoEM reconstruction of CD40 in complex with the Fab arms 30027P2, 21519P2, and 21520P2.

[0664] **Figure 24** shows an experimental timeline for the study described in Examples 21, 22, and 23.

[0665] **Figure 25** shows the effect of plasma cell depletion with anti-BCMAxCD3 bispecific antibody, FcRn blockade via efgartigimod alfa, B cell depletion with anti-CD19 and anti-CD20 antibodies (anti-CD19/CD20 antibodies), or combination thereof, on anti-AAV8 capsid IgG titers over time in mice previously treated with recombinant AAV8 vector.

[0666] **Figure 26** shows the effect of plasma cell depletion with anti-BCMAxCD3 bispecific antibody, FcRn blockade via efgartigimod alfa, B cell depletion with anti-CD19/CD20 antibodies, or combination thereof, on liver transduction 10 days following administration of a second AAV8 vector in mice previously treated with recombinant AAV8 vector, as measured by Taqman

quantitative real-time polymerase chain reaction (PCR) of green fluorescent protein (GFP) transgene DNA.

[0667] **Figure 27** shows the effect of plasma cell depletion with anti-BCMAxCD3 bispecific antibody, FcRn blockade via efgartigimod alfa, B cell depletion with anti-CD19/CD20 antibodies, or combination thereof, on liver transduction 10 days following administration of a second recombinant AAV8 vector in mice previously treated with a first recombinant AAV8 vector, as measured by Taqman quantitative real-time reverse-transcription PCR of GFP transgene RNA.

[0668] **Figures 28A-28B** show the effect of plasma cell depletion with anti-BCMAxCD3 bispecific antibody, FcRn blockade via efgartigimod alfa, B cell depletion with anti-CD19/CD20 antibodies, or combination thereof, on liver transduction 10 days following administration of a second recombinant AAV8 vector in mice previously treated with a first recombinant AAV8 vector, as measured by GFP immunohistochemical (IHC) staining of formalin-fixed paraffin embedded liver sections. **Figure 28A** shows GFP-positive area quantified using HALO software (Indica labs). **Figure 28B** shows representative images.

[0669] **Figures 29A-29J** show flow cytometry analysis of B cell and plasma cell frequencies and counts in bone marrow and spleen following treatment with anti-BCMAxCD3 bispecific antibody, FcRn blockade, anti-CD19/CD20 antibodies, or combinations thereof. **Figure 29A** shows bone marrow plasma cell frequencies. **Figure 29B** shows spleen plasma cell frequencies. **Figure 29C** shows spleen naïve B cell frequencies. **Figure 29D** shows spleen total memory B cell frequencies. **Figure 29E** shows spleen AAV-specific memory B cell frequencies. **Figure 29F** shows bone marrow plasma cell counts. **Figure 29G** shows spleen plasma cell counts. **Figure 29H** shows spleen naïve B cell counts. **Figure 29I** shows spleen total memory B cell counts. **Figure 29J** shows spleen AAV-specific memory B cell counts.

[0670] **Figure 30** shows the effect of efgartigimod on serum drug concentration of REGN5458 (BCMAxCD3).

[0671] **Figure 31** shows an experimental timeline for the study described in Example 25.

[0672] **Figures 32A-32B** show the effect of plasma cell depletion, B cell depletion, neonatal Fc receptor blockade, and combinations thereof, on naturally-occurring anti-AAV antibody titers in cynomolgus macaques. AAV8 neutralizing antibody (NAb) titer levels are presented for each treatment group over the duration of the study (**Figure 32A**) and specifically at Study Day 29 (**Figure 32B**).

[0673] **Figure 33** shows an experimental diagram for the non-human primate studies described in Examples 26 and 27.

[0674] **Figures 34A-34F** show the effect of prophylactic CD40 blockade on serum anti-AAV8 IgM, IgG, and neutralizing antibody titers in cynomolgus macaques.

[0675] **Figures 35A-35C** show the effect of prophylactic CD40 blockade on ability to systemically re-administer a second AAV8 vector in cynomolgus macaques.

[0676] **Figures 36A-36C** show the effect of prophylactic CD40 blockade on T cell-induced liver injury and expression of an immunogenic GFP transgene in liver.

DETAILED DESCRIPTION

Definitions

[0677] Before the present invention is described, it is to be understood that the invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0678] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0679] As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0680] The term "CD40," as used herein, refers to cluster of differentiation 40 (CD40/TNFRSF5), a co-stimulatory cell surface receptor that is part of the tumor necrosis factor (TNF) receptor superfamily. In some embodiments, the CD40 is a human CD40. In some embodiments, the CD40 protein comprises the amino acid sequence of human CD40 set forth in UniProt Accession No. Q09LL4.

[0681] The term "antigen-binding molecule" includes antibodies and antigen-binding fragments of antibodies, including multispecific antibodies, e.g., bispecific antibodies.

[0682] The term "antibody," as used herein, refers to an antigen-binding molecule or molecular complex comprising a set of complementarity determining regions (CDRs) that specifically bind to or interact with a particular antigen (e.g., CD40). The term "antibody," as used herein, includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers

thereof (*e.g.*, IgM). In a typical antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In some embodiments, the FRs of the antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0683] Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, but are not limited to, the Kabat definition, the Chothia definition, the AbM definition (enhanced Chothia or Martin), the IMGT definition, and the Honneger definition (Aho). In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat et al., "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Chothia et al., *J Mol Biol* (1987), 4:901–17; Al-Lazikani et al., J. Mol. Biol. 273:927-948 (1997); and Martin et al., Proc. Natl. Acad. Sci. USA 86:9268-9272 (1989); see also, Dondelinger et al., Front. Immunol. (2018), 9:2278, doi:10.3389/fimmu.2018.02278. Public databases are also available for identifying CDR sequences within an antibody.

[0684] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, "antigen-binding domain," and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial

sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0685] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g., monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0686] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0687] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-

binding fragment of an antibody may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

[0688] The term "antibody," as used herein, also includes multispecific (e.g., bispecific) antibodies. A multispecific antibody or antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. In some embodiments, a multispecific antibody (e.g., bispecific antibody) has an arm that binds to a first epitope of an antigen and an arm that binds to a second epitope of the same antigen.

[0689] Any multispecific antibody format may be adapted for use in the context of an antibody or antigen-binding fragment of an antibody of the present disclosure using routine techniques available in the art. For example, the present disclosure includes bispecific antibodies wherein one arm of an immunoglobulin is specific for a first epitope of CD40, and the other arm of the immunoglobulin is specific for a second epitope of CD40. Exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, e.g., scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (e.g., common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED) body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab^2 bispecific formats (*see*, *e.g.*, Klein *et al.* 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, e.g., wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (*See*, *e.g.*, Kazane *et al.*, *J. Am. Chem. Soc.* [Epub: Dec. 4, 2012]).

[0690] The term "human antibody," as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0691] The term "recombinant antibody," as used herein, is intended to include all antibodies

that are prepared, expressed, created or isolated by recombinant means. The term includes, but is not limited to, antibodies expressed using a recombinant expression vector transfected into a host cell (e.g., Chinese hamster ovary (CHO) cell) or cellular expression system, antibodies isolated from a recombinant, combinatorial human antibody library, and antibodies isolated from a non-human animal (e.g., a mouse, such as a mouse that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor et al. (1992) *Nucl. Acids Res.* 20:6287-6295). In some embodiments, the recombinant antibody is a recombinant human antibody. In some embodiments, recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0692] An "isolated antibody" refers to an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody." An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0693] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about $1x10^{-6}$ M or less, e.g., 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M (a smaller K_D denotes a tighter binding). Methods for determining whether an antibody specifically binds to an antigen are known in the art and include, for example, equilibrium dialysis, surface plasmon resonance (e.g., BIACORE™), bio-layer interferometry assay (e.g., Octet® HTX biosensor), solution-affinity ELISA, and the like. In some embodiments, specific binding is measured in a surface plasmon resonance assay, e.g., at 25°C or 37°C. An antibody or antigen-binding fragment that specifically binds an antigen from one species may or may not have cross-reactivity to other antigens, such as an orthologous antigen from another species.

[0694] The term "K_D," as used herein, refers to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0695] The term "surface plasmon resonance," as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Cytiva, Marlborough, MA).

[0696] The term "epitope," as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be either linear or discontinuous (e.g., conformational). A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups and, in some embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics. Epitopes may also be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. An epitope typically includes at least 3, and more usually, e.g., at least 5 or at least 8-10 amino acids, in a unique spatial conformation.

[0697] Methods for determining the epitope of an antigen-binding protein, e.g., an antibody or antigen-binding fragment, include alanine scanning mutational analysis, peptide blot analysis (Reineke, *Methods Mol Biol* 2004, 248:443-463), peptide cleavage analysis, crystallographic studies, and nuclear magnetic resonance (NMR) analysis. In addition, methods such as epitope exclusion, epitope extraction, and chemical modification of antigens can be employed (Tomer, *Prot Sci* 2000, 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antigen-binding protein (e.g., an antibody or antigen-binding fragment) interacts is hydrogen/deuterium exchange detected by mass spectrometry (HDX). See, e.g., Ehring, *Analytical Biochemistry* 1999, 267:252-259; Engen and Smith, *Anal Chem* 2001, 73:256A-265A.

[0698] The term "competes," as used in reference to competing for binding, refers to an antigen-binding protein (e.g., antibody or antigen-binding fragment) that binds to an antigen and

inhibits or blocks the binding of another antigen-binding protein (e.g., antibody or antigen-binding fragment) to the antigen. Unless otherwise stated, the term also includes competition between two antigen-binding proteins (e.g., antibodies) in both orientations, i.e., a first antigen that binds an antigen and blocks binding of the antigen by a second antibody, and vice versa. Thus, in some embodiments, competition occurs in one such orientation. In some embodiments, the first antigen-binding protein (e.g., antibody) and second antigen-binding protein (e.g., antibody) may bind to the same epitope. Alternatively, the first and second antigen-binding proteins (e.g., antibodies) may bind to different epitopes, which may be overlapping or non-overlapping, wherein binding of one antigen-binding protein inhibits or blocks the binding of the second antigen-binding protein, e.g., via steric hindrance. Competition between antigen-binding proteins may be measured by methods known in the art, e.g., by a real-time, label-free bio-layer interferometry assay.

[0699] The terms "protein," "polypeptide," and "peptide," used interchangeably herein, include polymeric forms of amino acids of any length, including coded and non-coded amino acids and chemically or biochemically modified or derivatized amino acids. The terms also include polymers that have been modified, such as polypeptides having modified peptide backbones. The term "domain" refers to any part of a protein or polypeptide having a particular function or structure.

[0700] The terms "nucleic acid" and "polynucleotide," used interchangeably herein, include polymeric forms of nucleotides of any length, including ribonucleotides, deoxyribonucleotides, or analogs or modified versions thereof. They include single-, double-, and multi-stranded DNA or RNA, genomic DNA, cDNA, DNA-RNA hybrids, and polymers comprising purine bases, pyrimidine bases, or other natural, chemically modified, biochemically modified, non-natural, or derivatized nucleotide bases.

[0701] In the context of the present disclosure, the term "neutralizing antibody" or "nAb" refers to an antibody that binds to a pathogen (e.g., a virus) and interferes with its ability to infect a cell. Non-limiting examples of neutralizing antibodies include antibodies that bind to a viral particle and inhibit successful transduction, e.g., one or more steps selected from binding, entry, trafficking to the nucleus, and transcription of the viral genome. Some neutralizing antibodies may block a virus at the post-entry step.

[0702] The term "immune response" refers to a response of a cell of the immune system (e.g., a B-cell, T-cell, macrophage or polymorphonucleocyte) to a stimulus such as an immunogen, e.g., antigen (e.g., a viral antigen). Active immune responses can involve differentiation and proliferation of immunocompetent cells, which leads to synthesis of antibodies or the

development of cell-mediated reactivity, or both. An active immune response can be mounted by the host after exposure to an antigen (e.g., by infection or by vaccination). An active immune response can be contrasted with passive immunity, which can be acquired through the transfer of substances such as, e.g., an antibody, a transfer factor, a thymic graft, and/or a cytokine, from an actively immunized host to a non-immune host.

[0703] The term "expression vector" or "expression construct" or "expression cassette" refers to a recombinant nucleic acid containing a desired coding sequence operably linked to appropriate nucleic acid sequences necessary for the expression of the operably linked coding sequence in a particular host cell or organism. Nucleic acid sequences necessary for expression in prokaryotes usually include a promoter, an operator (optional), and a ribosome binding site, as well as other sequences. Eukaryotic cells are generally known to utilize promoters, enhancers, and termination and polyadenylation signals, although some elements may be deleted and other elements added without sacrificing the necessary expression.

[0704] The term "viral vector" refers to a recombinant nucleic acid that includes at least one element of viral origin and includes elements sufficient for or permissive of packaging into a viral vector particle. The vector and/or particle can be utilized for the purpose of transferring DNA, RNA, or other nucleic acids into cells either *ex vivo* or *in vivo*. Numerous forms of viral vectors are known.

[0705] The terms "viral element" and "viral component" are used herein to refer to viral genes (e.g., genes encoding polymerase or structural proteins) or other elements of the viral genome (e.g., packaging signals, regulatory elements, LTRs, ITRs, etc.).

[0706] The term "capsid protein," "Cap protein," and the like, includes a protein that is part of the capsid of the virus.

[0707] The term "isolated" with respect to proteins, nucleic acids, and cells includes proteins, nucleic acids, and cells that are relatively purified with respect to other cellular or organism components that may normally be present *in situ*, up to and including a substantially pure preparation of the protein, nucleic acid, or cell. The term "isolated" may include proteins and nucleic acids that have no naturally occurring counterpart or proteins or nucleic acids that have been chemically synthesized and are thus substantially uncontaminated by other proteins or nucleic acids. The term "isolated" may include proteins, nucleic acids, or cells that have been separated or purified from most other cellular components or organism components with which they are naturally accompanied (e.g., but not limited to, other cellular proteins, nucleic acids, or cellular or extracellular components).

[0708] The term "heterologous" when used in the context of a nucleic acid or a protein indicates that the nucleic acid or protein comprises at least two segments that do not naturally occur together in the same molecule. For example, the term "heterologous," when used with reference to segments of a nucleic acid or segments of a protein, indicates that the nucleic acid or protein comprises two or more sub-sequences that are not found in the same relationship to each other (e.g., joined together) in nature. As one example, a "heterologous" region of a nucleic acid vector is a segment of nucleic acid within or attached to another nucleic acid molecule that is not found in association with the other molecule in nature. For example, a heterologous region of a nucleic acid vector could include a coding sequence flanked by a heterologous promoter not found in association with the coding sequence in nature. Likewise, a "heterologous" region of a protein is a segment of amino acids within or attached to another peptide molecule that is not found in association with the other peptide molecule in nature (e.g., a fusion protein, or a protein with a tag). Similarly, a nucleic acid or protein can comprise a heterologous label or a heterologous secretion or localization sequence.

[0709] A "promoter" is a regulatory region of DNA usually comprising a TATA box capable of directing RNA polymerase II to initiate RNA synthesis at the appropriate transcription initiation site for a particular polynucleotide sequence. A promoter may additionally comprise other regions which influence the transcription initiation rate. The promoter sequences disclosed herein modulate transcription of an operably linked polynucleotide. A promoter can be active in one or more of the cell types disclosed herein (e.g., a eukaryotic cell, a non-human mammalian cell, a human cell, a rodent cell, a pluripotent cell, a one-cell stage embryo, a differentiated cell, or a combination thereof). A promoter can be, for example, a constitutively active promoter, a conditional promoter, an inducible promoter, a temporally restricted promoter (e.g., a developmentally regulated promoter), or a spatially restricted promoter (e.g., a cell-specific or tissue-specific promoter). Examples of promoters can be found, for example, in WO 2013/176772, herein incorporated by reference in its entirety for all purposes.

[0710] A constitutive promoter is one that is active in all tissues or particular tissues at all developing stages. Examples of constitutive promoters include the human cytomegalovirus immediate early (hCMV), mouse cytomegalovirus immediate early (mCMV), human elongation factor 1 alpha (hEF1α), mouse elongation factor 1 alpha (mEF1α), mouse phosphoglycerate kinase (PGK), chicken beta actin hybrid (CAG or CBh), SV40 early, and beta 2 tubulin promoters.

[0711] Examples of inducible promoters include, for example, chemically regulated promoters and physically-regulated promoters. Chemically regulated promoters include, for example,

alcohol-regulated promoters (e.g., an alcohol dehydrogenase (alcA) gene promoter), tetracycline-regulated promoters (e.g., a tetracycline (tet)-responsive promoter, a tetracycline operator sequence (tetO), a tet-On promoter, or a tet-Off promoter), steroid-regulated promoters (e.g., a rat glucocorticoid receptor, a promoter of an estrogen receptor, or a promoter of an ecdysone receptor), or metal-regulated promoters (e.g., a metalloprotein promoter). Physically-regulated promoters include, for example, temperature-regulated promoters (e.g., a heat shock promoter) and light-regulated promoters (e.g., a light-inducible promoter or a light-repressible promoter).

[0712] Tissue-specific promoters can be, for example, neuron-specific promoters or glial-specific promoters or muscle-specific promoters.

[0713] Developmentally-regulated promoters include, for example, promoters active only during an embryonic stage of development, or only in an adult cell.

[0714] "Operable linkage" or being "operably linked" includes juxtaposition of two or more components (e.g., a promoter and another sequence element) such that both components function normally and allow the possibility that at least one of the components can mediate a function that is exerted upon at least one of the other components. For example, a promoter can be operably linked to a coding sequence if the promoter controls the level of transcription of the coding sequence in response to the presence or absence of one or more transcriptional regulatory factors. Operable linkage can include such sequences being contiguous with each other or acting *in trans* (e.g., a regulatory sequence can act at a distance to control transcription of the coding sequence).

[0715] The term "*in vitro*" includes artificial environments and to processes or reactions that occur within an artificial environment (e.g., a test tube or an isolated cell or cell line). The term "*in vivo*" includes natural environments (e.g., a cell, organism, or body) and to processes or reactions that occur within a natural environment. The term "*ex vivo*" includes cells that have been removed from the body of an individual and processes or reactions that occur within such cells.

[0716] The term "fusogen" or "fusogenic molecule" is used herein to refer to any molecule that can trigger membrane fusion when present on the surface of a virus particle. A fusogen can be, for example, a protein (e.g., a viral glycoprotein) or a fragment, mutant or derivative thereof.

[0717] The term "oncolytic virus" is used herein to refer to a virus that is capable of infecting and replicating in a tumor cell such that the tumor cell may be killed. The oncolytic virus may be replication competent. As a non-limiting example, the oncolytic virus may comprise a

rhabdovirus, i.e., any of a group of viruses comprising the family *Rhabdoviridae*, e.g., a vesicular stomatitis virus (VSV).

[0718] The term "T cell" is used herein in its broadest sense to refer to all types of immune cells expressing CD3, including T-helper cells (CD4+ cells), cytotoxic T-cells (CD8+ cells), T-regulatory cells (Treg), and natural killer (NK)-T cells.

[0719] "Retargeting" or "redirecting" may include a scenario in which a wildtype particle targets several cells within a tissue and/or several organs within an organism, and general targeting of the tissue or organs is reduced or abolished by insertion of the heterologous amino acid, and retargeting to more a specific cell in the tissue or a specific organ in the organism is achieved with the targeting ligand (e.g., via a targeting ligand) that binds a marker expressed by the specific cell. Such retargeting or redirecting may also include a scenario in which the wildtype particle targets a tissue, and targeting of the tissue is reduced to or abolished by insertion of the heterologous amino acid, and retargeting to a completely different tissue is achieved with the targeting ligand.

[0720] The term "wild type" or "wild-type" includes entities having a structure and/or activity as found in a normal (as contrasted with mutant, diseased, altered, or so forth) state or context. Wild type genes and polypeptides often exist in multiple different forms (e.g., alleles).

[0721] "Exogenous" molecules or sequences include molecules or sequences that are not normally present in a cell in that form or that are introduced into a cell from an outside source. Normal presence includes presence with respect to the particular developmental stage and environmental conditions of the cell. An exogenous molecule or sequence, for example, can include a mutated version of a corresponding endogenous sequence within the cell, such as a humanized version of the endogenous sequence, or can include a sequence corresponding to an endogenous sequence within the cell but in a different form (i.e., not within a chromosome). In contrast, endogenous molecules or sequences include molecules or sequences that are normally present in that form in a particular cell at a particular developmental stage under particular environmental conditions.

[0722] "Specific binding pair," "binding pair," "protein:protein binding pair," and the like, includes two members (e.g., a first member (e.g., a first polypeptide) and a second cognate member (e.g., a second polypeptide)) that interact to form a bond (e.g., a non-covalent bond between a first member epitope and a second member antigen-binding portion of an antibody that recognizes the epitope; a covalent bond between e.g., proteins capable of forming isopeptide bonds; split inteins that recognize each other and, through the process of protein trans-splicing, mediate ligation of the flanking proteins and their own removal). In some

embodiments, the term "cognate" refers to components that function together. Epitopes and cognate antibodies thereto, particularly epitopes that may also act as a detectable label (e.g., c-myc) are well-known in the art. Specific protein:protein binding pairs capable of interacting to form a covalent isopeptide bond are reviewed in Veggiani et al. (2014) *Trends Biotechnol.* 32:506, and include peptide:peptide binding pairs such as SpyTag:SpyCatcher, SpyTag002:SpyCatcher002; SpyTag:Ktag; isopeptag:pilin C, SnoopTag:SnoopCatcher, etc., and variants thereof, e.g., SpyTag003:SpyCatcher003. Generally, a first member of a protein:protein binding pair refers to member of a protein:protein binding pair, which is generally less than 30 amino acids in length, and which forms a spontaneous covalent isopeptide bond with the second cognate protein, wherein the second cognate protein is generally larger, but may also be less than 30 amino acids in length such as in the SpyTag:Ktag system.

[0723] The terms "substantial identity" and "substantially identical," as used with reference to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, e.g., at least 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99%, of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[0724] As applied to polypeptides, the terms "substantial identity" and "substantially identical" mean that two peptide sequences, when optimally aligned, share at least about 90% sequence identity, e.g., at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity. In some embodiments, residue positions that are not identical differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein.

[0725] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from

different species of organisms or between a wild-type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson, 2000 supra). Another preferred algorithm when comparing a sequence of the disclosure to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. (See, e.g., Altschul et al., 1990, *J. Mol. Biol.* 215: 403-410 and 1997 *Nucleic Acids Res.* 25:3389-3402).

[0726] A "variant" of a polypeptide, such an immunoglobulin, VH, VL, heavy chain, light chain, or CDR comprising an amino acid sequence specifically set forth herein, refers to a polypeptide comprising an amino acid sequence that is at least about 70%-99.9% (e.g., at least 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.5, or 99.9%) identical to the reference polypeptide sequence (e.g., as set forth in the sequence listing below), when the comparison is performed by a BLAST algorithm wherein the parameters of the algorithm are selected to give the largest match between the respective sequences over the entire length of the respective reference sequences. In some embodiments, a variant of a polypeptide includes a polypeptide having the amino acid sequence of a reference polypeptide sequence (e.g., as set forth in the sequence listing below) but for one or more (e.g., 1 to 10, or less than 20, or less than 10) missense mutations (e.g., conservative substitutions), nonsense mutations, deletions, or insertions.

[0727] The term "effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a subject in need thereof. Note that when a combination of active ingredients is administered, the effective amount of the combination may or may not include amounts of each ingredient that would have been effective if administered individually. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the particular drug or drugs employed, the mode of administration, and the like.

[0728] The phrase "pharmaceutically acceptable" as used in connection with compositions described herein, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (e.g., a human). Preferably, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S.

Pharmacopeia or other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

[0729] The terms "treat" or "treatment" of a state, disorder or condition include: (1) preventing, delaying, or reducing the incidence and/or likelihood of the appearance of at least one clinical or sub-clinical symptom of the state, disorder or condition developing in a subject that may be afflicted with or predisposed to the state, disorder or condition, but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition; (2) inhibiting the state, disorder or condition, i.e., arresting, reducing or delaying the development of the disease or a relapse thereof or at least one clinical or sub-clinical symptom thereof; or (3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or sub-clinical symptoms. The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician.

[0730] An "individual" or "subject" or "animal" refers to humans, veterinary animals (e.g., cats, dogs, cows, horses, sheep, pigs, etc.) and experimental animal models of diseases (e.g., mice, rats, monkeys (also referred to as non-human primates (NHPs) herein), e.g., cynomolgus macaques). In a preferred embodiment, the subject is a human

CD40 Antigen-Binding Molecules

[0731] In one aspect, the present disclosure relates to antigen-binding molecules, including monospecific, bispecific, and multispecific antibodies, that bind to CD40. In some embodiments, the antigen-binding molecule is a monospecific anti-CD40 antibody. In some embodiments, the antigen-binding molecule is a multispecific (e.g., bispecific) antibody. Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. *See*, *e.g.,* Tutt *et al.,* 1991, *J. Immunol.* 147:60-69; Kufer *et al.,* 2004, *Trends Biotechnol.* 22:238-244. In some embodiments, the CD40 antibodies of the present disclosure can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment, to produce a bispecific or a multispecific antibody with a second binding specificity. In some embodiments, the multispecific antibody contains an antigen-binding domain that is specific for CD40 and an antigen-binding domain that is specific for another antigen (i.e., not CD40). In some embodiments, the multispecific antibody contains an antigen-binding domain

that is specific for a first epitope of CD40 and an antigen-binding domain that is specific for a second epitope of CD40.

Monospecific Anti-CD40 Antibodies

[0732] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of 2/10, 22/10, and 32/10. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0733] In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises:

(a) an HCDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 24, and 34;

(b) an HCDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 26, and 36;

(c) an HCDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 28, and 38;

(d) an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12;

(e) an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14; and

(f) an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0734] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO:

12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0735] In some embodiments, the anti-CD40 antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the anti-CD40 antibody comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 4, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 6, an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 8, an LCDR1 consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 consisting of the amino acid sequence of SEQ ID NO: 16.

[0736] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 2; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 2. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

[0737] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 18; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising

or consisting of the amino acid sequence of SEQ ID NO: 18. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0738] In some embodiments, the anti-CD40 antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the anti-CD40 antibody comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 24, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 26, an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 28, an LCDR1 consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 consisting of the amino acid sequence of SEQ ID NO: 16.

[0739] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 22; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 22. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

[0740] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 30; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 30. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0741] In some embodiments, the anti-CD40 antibody comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the anti-CD40 antibody comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 34, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 36, an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 38, an LCDR1 consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 consisting of the amino acid sequence of SEQ ID NO: 16.

[0742] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 32; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 32. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

[0743] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 40; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 40. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0744] In some embodiments, the anti-CD40 antibody has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to 30027P2. In some embodiments, the anti-CD40 antibody has the amino acid sequence of 30027P2.

[0745] In some embodiments, the anti-CD40 antibody has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to 21519P2. In some embodiments, the anti-CD40 antibody has the amino acid sequence of 21519P2.

[0746] In some embodiments, the anti-CD40 antibody has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to 21520P2. In some embodiments, the anti-CD40 antibody comprises or consists of the amino acid sequence of 21520P2.

[0747] Other CD40 antigen-binding molecules that can be used in the compositions, combinations, kits, or methods disclosed herein include other known anti-CD40 antibodies. Non-limiting examples of additional anti-CD40 antibodies include CD40 Monoclonal Antibody (1C10) (eBioscience™), CD40 Monoclonal Antibody (HM40-3) (eBioscience™), CD40 Monoclonal Antibody (5C3) (eBioscience™), CD40 Monoclonal Antibody (9G10) (Invitrogen), CD40 Monoclonal Antibody (3/23) (Invitrogen), CD40 Monoclonal Antibody (HB14) (Invitrogen), CD40 Polyclonal Antibody (Invitrogen), CD40 Monoclonal Antibody (OTI1F12), TrueMAB™ (OriGene), CD40 Recombinant Rabbit Monoclonal Antibody (5V8X7) (Invitrogen), CD40 Monoclonal Antibody (LOB7/6) (Invitrogen), CD40 Monoclonal Antibody (5C3) (Invitrogen), CD40 Monoclonal Antibody (HI40a) (Invitrogen), CD40 Monoclonal Antibody (IL-A156) (Invitrogen), CD40 Monoclonal Antibody (C7) (Invitrogen), CD40 Polyclonal Antibody (Invitrogen, e.g., Cat # PA5-111025, Cat #PA5-111024, Cat #PA5-109301, Cat #PA5-117850, Cat #PA5-27419, Cat #PA5-78980, Cat #PA1-31075), CD40 Monoclonal Antibody (3/23) (Invitrogen), CD40 Monoclonal Antibody (HB14) (Invitrogen), CD40 Recombinant Rabbit Monoclonal Antibody (Bethyl Laboratories), CD40 Monoclonal Antibody (OTI8B8), TrueMAB™ (OriGene), CD40 Monoclonal Antibody (OTI1F12), TrueMAB™ (OriGene), CD40 Monoclonal Antibody (OTI5C9), TrueMAB™ (OriGene), CD40 Monoclonal Antibody (UMAB255), UltraMAB™ (OriGene), CD40 Monoclonal Antibody (2A8G5) (Proteintech), CD40 Monoclonal Antibody (G28.5) (Proteintech), CD40 Monoclonal Antibody (1C10) (Proteintech), CD40 Monoclonal Antibody (G28.5) (Proteintech), CD40 Monoclonal Antibody (2A8G5) (Proteintech), CD40 Monoclonal Antibody (UMAB183), UltraMAB™ (OriGene), CD40 Monoclonal Antibody (UMAB183), UltraMAB™ (OriGene), CD40 Monoclonal Antibody (HB14) (AbboMax), CD40 Monoclonal Antibody (1G1) (Abnova), CD40 Polyclonal Antibody (AbboMax, Cat #500-3704), CD40 Monoclonal Antibody (FGK45) (Leinco Technologies), CD40 Monoclonal Antibody (3D9) (Abnova), and CD40 Monoclonal Antibody (2H8) (Abnova).

[0748] In some embodiments, the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof. The antagonistic anti-CD40 antibody may comprise any antagonistic anti-CD40 antibody known in the art. Non-limiting examples of antagonistic anti-CD40 antibodies include iscalimab (also known as CFZ533) disclosed in Kahaly et al. (2019) J. Endocr. Sco. 3:doi.org/10.1210/js.2019-0R19-6, Fisher et al. (2017) Arthritis Rheumatol. 69:1784, Farkash et al. (2019) Am. J. Transplant. 19:632, U.S. Pat. No. US 8,828,396, International Patent Application Publication No. WO 2012/075111, and clinical trial NCT02291029 sponsored by Novartis Pharmaceuticals; ravagalimab (also known as ABBV-323 and Ab102) disclosed in International Patent Application Publication No. WO 2016/196314 and U.S. Patent Application Publication No. US 2022/0289858; BI-655064 disclosed in Visvannathan et al. (2016) Arthritis Rheumatol. 68:1588, U.S. Pat. No. 8,591,900, and clinical trial NCT03385564 sponsored by Boehringer Ingelheim; bleselumab (also known as ASKP1240 or 341G2) disclosed in Anil et al. (2018) Biopharm. Drug Dispos. 39:245-255, Harland et al. (2017) Am. J. Transplant. 17:159-171, U.S. Pat. Nos. 8,716,451 and 8,568,725, and clinical trials NCT01585233 and NCT02921789 sponsored by Astellas Pharma; ch5D12 disclosed in Kasran et al. (2005) Aliment. Pharmacol. Ther. 22:111-122 and U.S. Patent Application Publication No. US 2008/0085531; lucatumumab (also known as HCD122 or CHIR-12.12) disclosed in Bensinger et al. (2012) British J. Haematology 159:58-66, Byrd et al. (2012) Leuk. Lymphoma 53:10.3109/10428194.2012.681655, International Patent Application Publication No. WO 2005/044854, U.S. Patent Application Publication No. US 2007/0110754 and U.S. Pat. No. US 8,828,396; CHIR-5.9 disclosed in International Patent Application Publication No. WO 2005/044854 and U.S. Pat. No. 8,637,032; abiprubart [KPL-404] disclosed in clinical trial NCT04497662 sponsored by Kiniksa Pharmaceuticals, Ltd. as well as in U.S. Patent Application Publication Nos. US 2023/0287132, US 2023/0203179, US 2023/0183367, and US 2023/0279135; BIIB063 disclosed in Musselli et al. (2017) 2017 ACR/ARHP Annual Meeting Abstract and International Patent Application Publication No. WO 2016028810; V19 and V15 disclosed in U.S. Patent Application Publication No. US 2022/0135694; h2C10 and variants thereof disclosed in U.S. Pat. No. 11,439,706; FFP104 (also known as PG102) disclosed in U.S. Pat. Nos. 8,669,352 and 11,396,552, International Patent Application Publication No. WO 2001/024823, U.S. Patent Application Publication No. US 2008/0085531, Bankert et al. (2015) J. Immunol. 194:4319-4327, and clinical trials NCT02193360 and NCT02465944 sponsored by Fast Forward Pharmaceuticals; Ab101 disclosed in U.S. Patent Application Publication No. US 2022/0289858; Antibody A, antibody B, Antibody C, disclosed in U.S. Pat. No. 11,242,394; G28.5 disclosed in International Patent Application Publication No. WO 2016028810; BMS3h-

37, BMS3h-38, BMS3h-56, and BMS3h-198 disclosed in International Patent Application Publication No. WO2012145673A1,and Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3], and Y12XX-hz42 [Vh-hzl4;Vk-hz3] disclosed in International Patent Application Publication No. WO2020/106620A1, the contents of each of which are herein incorporated by reference in their entirety. An additional CD40 antibody useful in certain embodiments of the methods and compositions provided herein is teneliximab. Additional CD40 antagonist antibodies useful in certain embodiments of the methods and compositions provided herein are disclosed in, for example, International Patent Application Publication Nos. WO 02/11763, WO 02/28481, WO 03/045978, WO 03/029296, WO 03/028809, WO 2005/044854, WO 2006/073443, WO 2007/124299, WO 2011/123489, WO 2016/196,314, WO 2017/040566, WO 2017/060242, WO 2018/217976, WO2019/156565, WO 2020/144605, WO 2020/106620, WO 2020/006347, U.S. Patent Application Publication Nos. US 2020/0291123, US 2017/0158771, US 2008/0057070, and U.S. Pat. Nos. 5,874,082, 7,063,845, 9,125,893, 8,669,352, 9,598,494, 11,254,750, 11,780,927, 11,220,550, 11,202,827, 10,111,958, 11,242,397, 8,591,900, 9,475,879, 10,174,121, the contents of each of which are herein incorporated by reference in their entirety.

[0749] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 109/113. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0750] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 110, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116.

[0751] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 109; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 113. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 109. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 113.

[0752] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 117; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 118. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 117. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 118. In some embodiments, the anti-CD40 antibody is abiprubart (also known as KPL-404).

Abiprubart [KPL-404] HCDR1
YTFTNYWMH (SEQ ID NO: 110)

Abiprubart [KPL-404] HCDR2
YINPSNDYTKYNQKFKD (SEQ ID NO: 111)

Abiprubart [KPL-404] HCDR3
QGFPY (SEQ ID NO: 112)

Abiprubart [KPL-404] LCDR1
SASSSVSYMH (SEQ ID NO: 114)

Abiprubart [KPL-404] LCDR2
DTSKLAS (SEQ ID NO: 115)

Abiprubart [KPL-404] LCDR3
HQLSSDPFT (SEQ ID NO: 116)

Abiprubart [KPL-404] HCVR
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYINPSNDYTKYN
QKFKDRATLTADKSANTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO:
109)

Abiprubart [KPL-404] LCVR
EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRRWIYDTSKLASGVPARFSG
SGSGTDYTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIK (SEQ ID NO: 113)

Abiprubart [KPL-404] HC
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYINPSNDYTKYN
QKFKDRATLTADKSANTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSSASTKGPSVF
PLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP
SSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISR
TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNG
KEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL
SLSPGK (SEQ ID NO: 117)

Abiprubart [KPL-404] LC
EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRRWIYDTSKLASGVPARFSG
SGSGTDYTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGT
ASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVY
ACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 118)

[0753] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 57/61. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat

definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0754] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 58, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64.

[0755] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 57; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 61. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 57. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 61.

[0756] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 65; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 66. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 65. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-CD40 antibody is iscalimab.

Iscalimab [CFZ533] HCDR1
SYGMH (SEQ ID NO: 58)

Iscalimab [CFZ533] HCDR2

VISYEESNRYHADSVKG (SEQ ID NO: 59)

Iscalimab [CFZ533] HCDR3
DGGIAAPGPDY (SEQ ID NO: 60)

Iscalimab [CFZ533] LCDR1
RSSQSLLYSNGYNYLD (SEQ ID NO: 62)

Iscalimab [CFZ533] LCDR2
LGSNRAS (SEQ ID NO: 63)

Iscalimab [CFZ533] LCDR3
MQARQTPFT (SEQ ID NO: 64)

Iscalimab [CFZ533] HCVR
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYEESNRYHA
DSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDYWGQGTLVTVSS (SEQ
ID NO: 57)

Iscalimab [CFZ533] LCVR
DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQVLISLGSNRASGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIR (SEQ ID NO: 61)

Iscalimab [CFZ533] HC
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYEESNRYHA
DSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDYWGQGTLVTVSSASTK
GPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 65)

Iscalimab [CFZ533] LC

DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQVLISLGSNRASGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIRRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 66)

[0757] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 67/71. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0758] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 68, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74.

[0759] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 67; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 71. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 71.

[0760] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 75; and/or a light chain comprising an amino acid sequence

that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 76. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 75. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 76. In some embodiments, the anti-CD40 antibody is ravagalimab.

Ravagalimab [ABBV-323; Ab102] HCDR1
GFTFSDYGMN (SEQ ID NO: 68)

Ravagalimab [ABBV-323; Ab102] HCDR2
YISSGRGNIYYADTVKG (SEQ ID NO: 69)

Ravagalimab [ABBV-323; Ab102] HCDR3
SWGYFDV (SEQ ID NO: 70)

Ravagalimab [ABBV-323; Ab102] LCDR1
KSSQSLLNRGNQKNYLT (SEQ ID NO: 72)

Ravagalimab [ABBV-323; Ab102] LCDR2
WASTRES (SEQ ID NO: 73)

Ravagalimab [ABBV-323; Ab102] LCDR3
QNDYTYPLT (SEQ ID NO: 74)

Ravagalimab [ABBV-323; Ab102] HCVR
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSGRGNIYYAD TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQGTTVTVSS (SEQ ID NO: 67)

Ravagalimab [ABBV-323; Ab102] LCVR
DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNQKNYLTWFQQKPGQPPKLLIYWASTRESG VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGQGTKLEIK (SEQ ID NO: 71)

Ravagalimab [ABBV-323; Ab102] HC
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSGRGNIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQGTTVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDQL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHNHYTQK
SLSLSPGK (SEQ ID NO: 75)

Ravagalimab [ABBV-323; Ab102] LC
DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNQKNYLTWFQQKPGQPPKLLIYWASTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGQGTKLEIKRTVAAPSVFIFPPSD
EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 76)

[0761] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 77/81. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0762] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 78, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74.

[0763] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least

96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 77; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 81. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 77. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 81.

[0764] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 84; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 85. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 84. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 85. In some embodiments, the anti-CD40 antibody is BI-655064.

BI-655064 HCDR1
GFTFSDYGMH (SEQ ID NO: 78)

BI-655064 HCDR2
YISSGNRIIYYADTVKG (SEQ ID NO: 79)

BI-655064 HCDR3
QDGYRYAMDY (SEQ ID NO: 80)

BI-655064 LCDR1
KSSQSLLNSGNQKNYLT (SEQ ID NO: 82)

BI-655064 LCDR2
WTSTRES (SEQ ID NO: 83)

BI-655064 LCDR3

QNDYTYPLT (SEQ ID NO: 74)

BI-655064 HCVR
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSS (SEQ
ID NO: 77)

BI-655064 LCVR
DIVMTQSPDSLAVSLGEKVTINCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIYWTSTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVEIK
(SEQ ID NO: 81)

BI-655064 HC
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 84)

BI-655064 LC
DIVMTQSPDSLAVSLGEKVTINCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIYWTSTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)

[0765] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 86/90. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat

definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0766] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 87, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 92, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93.

[0767] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 86; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 90. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 86. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 90.

[0768] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 94; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 95. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 94. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 95. In some embodiments, the anti-CD40 antibody is bleselumab.

Bleselumab HCDR1
GGSISSPGYY (SEQ ID NO: 87)

Bleselumab HCDR2

IYKSGST (SEQ ID NO: 88)

Bleselumab HCDR3
RPVVRYFGWFDP (SEQ ID NO: 89)

Bleselumab LCDR1
QGISSA (SEQ ID NO: 91)

Bleselumab LCDR2
DAS (SEQ ID NO: 92)

Bleselumab LCDR3
QQFNSYPT (SEQ ID NO: 93)

Bleselumab HCVR
QLQLQESGPGLLKPSETLSLTCTVSGGSISSPGYYGGWIRQPPGKGLEWIGSIYKSGSTYHNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCTRPVVRYFGWFDPWGQGTLVTVSS (SEQ ID NO: 86)

Bleselumab LCVR
AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASNLESGVPSRFSG SGSGTDFTLTISSLQPEDFATYYCQQFNSYPTFGQGTKVEIK (SEQ ID NO: 90)

Bleselumab HC
QLQLQESGPGLLKPSETLSLTCTVSGGSISSPGYYGGWIRQPPGKGLEWIGSIYKSGSTYHNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCTRPVVRYFGWFDPWGQGTLVTVSSASTKG PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK (SEQ ID NO: 94)

Bleselumab LC

AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASNLESGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQFNSYPTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 95)

[0769] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 96/100. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0770] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 97, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103.

[0771] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 96; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 100. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 96. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 100. In some embodiments, the anti-CD40 antibody is ch5d12.

ch5D12 HCDR1
GFSLSRY (SEQ ID NO: 97)

ch5D12 HCDR2
WGGGS (SEQ ID NO: 98)

ch5D12 HCDR3
TDGDY (SEQ ID NO: 99)

ch5D12 LCDR1
RSSQSLVNSNGNTYLH (SEQ ID NO: 101)

ch5D12 LCDR2
KVSNRFS (SEQ ID NO: 102)

ch5D12 LCDR3
SQSTHVPWT (SEQ ID NO: 103)

ch5D12 HCVR
QVKLEESGPGLVAPSQSLSITCTVSGFSLSRYSVYWVRQPPGKGLEWLGMMWGGGSTDYNS ALKSRLSISKDTSKSQVFLKMNSLRTDDTAMYYCVRTDGDYWGQGTSVTVSS (SEQ ID NO: 96)

ch5D12 LCVR
ELQLTQSPLSLPVSLGDQASISCRSSQSLVNSNGNTYLHWYLQKPGQSPKLLIYKVSNRFSGVP DRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKLEIKR (SEQ ID NO: 100)

[0772] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 57/61. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0773] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 58, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64.

[0774] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 57; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 61. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 57. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 61.

[0775] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 104; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 66. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 104. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-CD40 antibody is lucatumumab.

Lucatumumab [HCD122 or CHIR-12.12] HCDR1
SYGMH (SEQ ID NO: 58)

Lucatumumab [HCD122 or CHIR-12.12] HCDR2
VISYEESNRYHADSVKG (SEQ ID NO: 59)

Lucatumumab [HCD122 or CHIR-12.12] HCDR3
DGGIAAPGPDY (SEQ ID NO: 60)

Lucatumumab [HCD122 or CHIR-12.12] LCDR1
RSSQSLLYSNGYNYLD (SEQ ID NO: 62)

Lucatumumab [HCD122 or CHIR-12.12] LCDR2
LGSNRAS (SEQ ID NO: 63)

Lucatumumab [HCD122 or CHIR-12.12] LCDR3
MQARQTPFT (SEQ ID NO: 64)

Lucatumumab [HCD122 or CHIR-12.12] HCVR
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYEESNRYHA
DSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDYWGQGTLVTVSS (SEQ
ID NO: 57)

Lucatumumab [HCD122 or CHIR-12.12] LCVR
DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQVLISLGSNRASGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIR (SEQ ID NO: 61)

Lucatumumab [HCD122 or CHIR-12.12] HC
QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYEESNRYHA
DSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDYWGQGTLVTVSSASTK
GPSVFPLAPASKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSS
VVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 104)

Lucatumumab [HCD122 or CHIR-12.12] LC
DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQVLISLGSNRASGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIRRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 66)

[0776] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 105/106. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0777] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 105; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 106. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 105. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 106.

[0778] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 107; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 108. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 107. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 108. In some embodiments, the anti-CD40 antibody is CHIR-5.9.

CHIR-5.9 HCVR

EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSP
SFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGTAAGRDYYYYYGMDVWGQGTTVTVS
S (SEQ ID NO: 105)

CHIR-5.9 LCVR
AIVMTQPPLSSPVTLGQPASISCRSSQSLVHSDGNTYLNWLQQRPGQPPRLLIYKFFRRLSGVP
DRFSGSGAGTDFTLKISRVEAEDVGVYYCMQVTQFPHTFGQGTRLEIK (SEQ ID NO: 106)

CHIR-5.9 HC
EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPGDSDTRYSP
SFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGTAAGRDYYYYYGMDVWGQGTTVTVS
SASTKGPSVFPLAPASKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLF
PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL
TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA
LHNHYTQKSLSLSPGK (SEQ ID NO: 107)

CHIR-5.9 LC
AIVMTQPPLSSPVTLGQPASISCRSSQSLVHSDGNTYLNWLQQRPGQPPRLLIYKFFRRLSGVP
DRFSGSGAGTDFTLKISRVEAEDVGVYYCMQVTQFPHTFGQGTRLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 108)

[0779] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 119/121. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0780] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 97, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103.

[0781] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 119; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 121. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 119. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 121.

[0782] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 123 or 124; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 125. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 123 or 124. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 125. In some embodiments, the anti-CD40 antibody is FFP104 (also known as PG102).

PG102 // FFP104 HCDR1
GFSLSRY (SEQ ID NO: 97)

PG102 // FFP104 HCDR2
WGGGSTD (SEQ ID NO: 120)

PG102 // FFP104 HCDR3

TDGDY (SEQ ID NO: 99)

PG102 // FFP104 LCDR1
RSSQSLANSNGNTYLH (SEQ ID NO: 122)

PG102 // FFP104 LCDR2
KVSNRFS (SEQ ID NO: 102)

PG102 // FFP104 LCDR3
SQSTHVPWT (SEQ ID NO: 103)

PG102 // FFP104 HCVR
QVKLQESGPGLVKPSETLSITCTVSGFSLSRYSVYWIRQPPGKGPEWMGMMWGGGSTDYST
SLKSRLTISKDTSKSQVSLKMNSLRTDDTAMYYCVRTDGDYWGQGTTVTVSS (SEQ ID NO:
119)

PG102 // FFP104 LCVR
ELQLTQSPLSLPVTLGQPASISCRSSQSLANSNGNTYLHWYLQRPGQSPRLLIYKVSNRFSGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGGGTKLEIKR (SEQ ID NO: 121)

PG102 // FFP104 HC
QVKLQESGPGLVKPSETLSITCTVSGFSLSRYSVYWIRQPPGKGPEWMGMMWGGGSTDYST
SLKSRLTISKDTSKSQVSLKMNSLRTDDTAMYYCVRTDGDYWGQGTTVTVSSASTKGPSVFPL
APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSCPAPEFLGGPSVFLFPPKPKDTLMISRTP
EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS
LGK (SEQ ID NO: 123)

QVKLQESGPGLVKPSETLSITCTVSGFSLSRYSVYWIRQPPGKGPEWMGMMWGGGSTDYST
SLKSRLTISKDTSKSQVSLKMNSLRTDDTAMYYCVRTDGDYWGQGTTVTVSSASTKGPSVFPL
APCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSS
SLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTP

EVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE
YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLS
LG (SEQ ID NO: 124)

PG102 // FFP104 LC
ELQLTQSPLSLPVTLGQPASISCRSSQSLANSNGNTYLHWYLQRPGQSPRLLIYKVSNRFSGVP
DRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGGGTKLEIKRTVAAPSVFIFPPSDE
QLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 125)

[0783] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 126/130. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0784] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 127, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133.

[0785] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 126; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 130. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 126. In some

embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 130.

[0786] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 134; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 135. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 134. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 135. In some embodiments, the anti-CD40 antibody is BIIB063.

BIIB063 HCDR1
TFPIE (SEQ ID NO: 127)

BIIB063 HCDR2
NFHPYNDDTKYNEKFKG (SEQ ID NO: 128)

BIIB063 HCDR3
RGKLPFDS (SEQ ID NO: 129)

BIIB063 LCDR1
RASQDISNYLN (SEQ ID NO: 131)

BIIB063 LCDR2
FTSRLRS (SEQ ID NO: 132)

BIIB063 LCDR3
QQDRKLPWT (SEQ ID NO: 133)

BIIB063 HCVR

EVQLVQSGAEVKKPGASVKVSCKASGYTFTTFPIEWVRQAPGQGLEWMGNFHPYNDDTKYN
EKFKGRVTLTADKSTSTAYMELSRLRSEDTAVYYCARRGKLPFDSWGQGTTVTVSS (SEQ ID
NO: 126)

BIIB063 LCVR
DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKVPKLLIYFTSRLRSGVPSRFSG
SGSGTDYTLTISSLQPEDVATYYCQQDRKLPWTFGQGTKLEIK (SEQ ID NO: 130)

BIIB063 HC
EVQLVQSGAEVKKPGASVKVSCKASGYTFTTFPIEWVRQAPGQGLEWMGNFHPYNDDTKYN
EKFKGRVTLTADKSTSTAYMELSRLRSEDTAVYYCARRGKLPFDSWGQGTTVTVSSASTKGP
SVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMI
SRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLN
GKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAV
EWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKS
LSLSLG (SEQ ID NO: 134)

BIIB063 LC
DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKVPKLLIYFTSRLRSGVPSRFSG
SGSGTDYTLTISSLQPEDVATYYCQQDRKLPWTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 135)

[0787] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3 amino acid sequences set contained within the HCVR amino acid sequence set forth in SEQ ID NO: 136. In some embodiments, the CDRs within the HCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR are identified according to the IMGT definition.

[0788] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 137, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 138, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 139.

[0789] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 136. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 136. In some embodiments, the anti-CD40 antibody is V19.

V19 HCDR1
RSAMG (SEQ ID NO: 137)

V19 HCDR2
AIGTRGGSTKYADSVKG (SEQ ID NO: 138)

V19 HCDR3
RGPGYPSAAIFQDEYHY (SEQ ID NO: 139)

V19 HCVR
QVQLQESGGGLVQAGGSLRLSCAASGRTFGRSAMGWFRQAPGKEREFVAAIGTRGGSTKYA
DSVKGRFTISTDNASNTVYLQMDSLKPEDTAVYRCAVRGPGYPSAAIFQDEYHYWGQGTQVT
VSS (SEQ ID NO: 136)

[0790] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3 amino acid sequences set contained within the HCVR amino acid sequence set forth in SEQ ID NO: 140. In some embodiments, the CDRs within the HCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR are identified according to the IMGT definition.

[0791] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 141, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 142, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 143.

[0792] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 140. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 140. In some embodiments, the anti-CD40 antibody is V15.

V15 HCDR1
SDTMG (SEQ ID NO: 141)

V15 HCDR2
SISSRGVREYADSVKG (SEQ ID NO: 142)

V15 HCDR3
GALGLPGYRPYNN (SEQ ID NO: 143)

V15 HCVR
EVQLQESGGGLVQAGGSLRLSCVTSGSAFSSDTMGWFRQAPGKQRELVASISSRGVREYAD
SVKGRFTISRDNAKNTVYLQMNSLQPEDTAVYYCNRGALGLPGYRPYNNWGQGTQVTVSS
(SEQ ID NO: 140)

[0793] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 109/113, 109/145, 109/148, 109/150, 144/113, 144/145, 144/148, 144/150, 146/113, 146/145, 146/148, 146/150, 147/113, 147/145, 147/148, 147/150, 149/113, 149/145, 149/148, or 149/150. In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within

the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 109/113, 144/145, 146/145, 147/148, or 149/150. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0794] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 110, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116.

[0795] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 109, 144, 146, 147, or 149; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 113, 145, 148, or 150. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 109, 144, 146, 147, or 149. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 113, 145, 148, or 150. In some embodiments, the anti-CD40 antibody is h2C10 or a variant thereof.

2C10 HCDR1
YTFTNYWMH (SEQ ID NO: 110)

2C10 HCDR2
YINPSNDYTKYNQKFKD (SEQ ID NO: 111)

2C10 HCDR3
QGFPY (SEQ ID NO: 112)

2C10 LCDR1

SASSSVSYMH (SEQ ID NO: 114)

2C10 LCDR2
DTSKLAS (SEQ ID NO: 115)

2C10 LCDR3
HQLSSDPFT (SEQ ID NO: 116)

2C10_h1 HCVR
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWMGYINPSNDYTKY NQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO: 144)

2C10_h2 HCVR
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWMGYINPSNDYTKY NQKFKDRVTITADKSASTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO: 146)

2C10_h3 HCVR
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYINPSNDYTKYN QKFKDRATLTADKSANTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO: 109)

2C10_l1 LCVR
EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGIPARFSGS GSGTDFTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIK (SEQ ID NO: 145)

2C10_l2 LCVR
EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRRWIYDTSKLASGVPARFSG SGSGTDYTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIK (SEQ ID NO: 113)

2C10HP HCVR

QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYINPSNDYTKYN QKFKDRATLTADKSANTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO: 109)

2C10HB1 HCVR
QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYINPSNDYTKYN QKFKDRATLTADTSTNTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO: 147)

2C10HB2 HCVR
QVQLVQSGAEVKKPGSSVKVSCKASGYTFTNYWMHWVRQAPGQGLEWIGYINPSNDYTKYN QKFKDKATITADESTNTAYMELSSLRSEDTAVYYCARQGFPYWGQGTLVTVSS (SEQ ID NO: 149)

2C10KP LCVR
EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRRWIYDTSKLASGVPARFSG SGSGTDYTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIK (SEQ ID NO: 113)

2C10KB1 LCVR
DIQMTQSPSTLSASVGDRVTITCSASSSVSYMHWYQQKPGKAPKLLIYDTSKLASGVPARFSG SGSGTEFTLTISSLQPDDFATYYCHQLSSDPFTFGQGTKVEVK (SEQ ID NO: 148)

2C10KB2 LCVR
EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGIPARFSGS GSGTDFTLTISSLEPEDFAVYYCHQLSSDPFTFGQGTKLEIK (SEQ ID NO: 150)

[0796] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 67/71. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or

LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0797] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 68, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74.

[0798] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 67; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 71. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 71.

[0799] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 151; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 76. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 151. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 76. In some embodiments, the anti-CD40 antibody is Ab101.

Ab101 HCDR1
GFTFSDYGMN (SEQ ID NO: 68)

Ab101 HCDR2
YISSGRGNIYYADTVKG (SEQ ID NO: 69)

Ab101 HCDR3
SWGYFDV (SEQ ID NO: 70)

Ab101 LCDR1
KSSQSLLNRGNQKNYLT (SEQ ID NO: 72)

Ab101 LCDR2
WASTRES (SEQ ID NO: 73)

Ab101 LCDR3
QNDYTYPLT (SEQ ID NO: 74)

Ab101 HCVR
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSGRGNIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQGTTVTVSS (SEQ ID
NO: 67)

Ab101 LCVR
DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNQKNYLTWFQQKPGQPPKLLIYWASTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGQGTKLEIK (SEQ ID NO: 71)

Ab101 HC
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSGRGNIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQGTTVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV
PSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPGK (SEQ ID NO: 151)

Ab101 LC
DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNQKNYLTWFQQKPGQPPKLLIYWASTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGQGTKLEIKRTVAAPSVFIFPPSD

EQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 76)

[0800] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 152/154. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0801] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 153, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74.

[0802] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 152; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 154. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 152. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 154.

[0803] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 155, 157, 158, or 159; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%

sequence identity to SEQ ID NO: 156. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 155, 157, 158, or 159. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 156. In some embodiments, the anti-CD40 antibody is Antibody A.

Antibody A HCDR1
DYGMH (SEQ ID NO: 153)

Antibody A HCDR2
YISSGNRIIYYADTVKG (SEQ ID NO: 79)

Antibody A HCDR3
QDGYRYAMDY (SEQ ID NO: 80)

Antibody A LCDR1
KSSQSLLNSGNQKNYLT (SEQ ID NO: 82)

Antibody A LCDR2
WTSTRES (SEQ ID NO: 83)

Antibody A LCDR3
QNDYTYPLT (SEQ ID NO: 74)

Antibody A HCVR
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD TVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYWAQGTLVTVSS (SEQ ID NO: 152)

Antibody A LCVR
DIVMTQSPDSLAVSLGERATMSCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIYWTSTRES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVEIK (SEQ ID NO: 154)

Antibody A HC

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYWAQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 155)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYWAQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 157)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYWAQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 158)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYWAQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS

DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 159)

Antibody A LC
DIVMTQSPDSLAVSLGERATMSCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIYWTSTRES
GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 156)

[0804] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 77/81. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0805] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 153, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74.

[0806] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 77; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 81. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 77. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 81.

[0807] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 160, 161, 162, or 84; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 85. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 160, 161, 162, or 84. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 85. In some embodiments, the anti-CD40 antibody is Antibody B.

Antibody B HCDR1
DYGMH (SEQ ID NO: 153)

Antibody B HCDR2
YISSGNRIIYYADTVKG (SEQ ID NO: 79)

Antibody B HCDR3
QDGYRYAMDY (SEQ ID NO: 80)

Antibody B LCDR1
KSSQSLLNSGNQKNYLT (SEQ ID NO: 82)

Antibody B LCDR2
WTSTRES (SEQ ID NO: 83)

Antibody B LCDR3
QNDYTYPLT (SEQ ID NO: 74)

Antibody B HCVR
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSS (SEQ ID NO: 77)

Antibody B LCVR
DIVMTQSPDSLAVSLGEKVTINCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIYWTSTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVEIK (SEQ ID NO: 81)

Antibody B HC
EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 160)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 161)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL
MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 162)

EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSGNRIIYYAD
TVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 84)

Antibody B LC
DIVMTQSPDSLAVSLGEKVTINCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIYWTSTRESG
VPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVEIKRTVAAPSVFIFPPS
DEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKA
DYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 85)

[0808] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 163/167. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0809] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 164, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170.

[0810] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 163; and/or

an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 167. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 163. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 167.

[0811] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 171, 173, 174, or 175; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 172. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 171, 173, 174, or 175. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 172. In some embodiments, the anti-CD40 antibody is Antibody C.

Antibody C HCDR1
GFNIKDYYVH (SEQ ID NO: 164)

Antibody C HCDR2
RIDPEDGDSKYAPKFQG (SEQ ID NO: 165)

Antibody C HCDR3
SYYVGTYGY (SEQ ID NO: 166)

Antibody C LCDR1
SASSSVSYML (SEQ ID NO: 168)

Antibody C LCDR2
STSNLAS (SEQ ID NO: 169)

Antibody C LCDR3

QQRTFYPYT (SEQ ID NO: 170)

Antibody C HCVR
QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDPEDGDSKYA
PKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYWGQGTLVTVSS (SEQ
ID NO: 163)

Antibody C LCVR
DIQMTQSPSSLSASVGDRVTITCSASSSVSYMLWFQQKPGKAPKLLIYSTSNLASGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCQQRTFYPYTFGGGTKVEIK (SEQ ID NO: 167)

Antibody C HC
QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDPEDGDSKYA
PKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 171)

QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDPEDGDSKYA
PKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYP
SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY
TQKSLSLSPGK (SEQ ID NO: 173)

QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDPEDGDSKYA
PKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYWGQGTLVTVSSASTKG
PSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFEGGPSVFLFPPKPKDTL

MISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDW
LNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDI
AVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ
KSLSLSLGK (SEQ ID NO: 174)

QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDPEDGDSKYA
PKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYWGQGTLVTVSSASTKG
PSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSV
VTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ
DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPS
DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK (SEQ ID NO: 175)

Antibody C LC
DIQMTQSPSSLSASVGDRVTITCSASSSVSYMLWFQQKPGKAPKLLIYSTSNLASGVPSRFSGS
GSGTDFTLTISSLQPEDFATYYCQQRTFYPYTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTA
SVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYA
CEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 172)

[0812] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 176/177. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0813] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 176; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 177. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 176. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 177. In some embodiments, the anti-CD40 antibody is G28.5.

G28.5 HCVR
DIQLQQSGPGLVKPSQSLSLTCSVTGYSITTNYNWNWIRQFPGNKLEWMGYIRYDGTSEYTPS
LKNRVSITRDTSMNQFFLRLTSVTPEDTATYYCARLDYWGQGTSVTVSS (SEQ ID NO: 176)

G28.5 LCVR
DAVMTQNPLSLPVSLGDEASISCRSSQSLENSNGNTFLNWFFQKPGQSPQLLIYRVSNRFSGV
PDRFSGSGSGTDFTLKISRVEAEDLGVYFCLQVTHVPYTFGGGTTLEIK (SEQ ID NO: 177)

[0814] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 178/182. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0815] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 179, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185.

[0816] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 178; and/or

an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 182. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 178. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 182.

[0817] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 186; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 187. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 186. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 187. In some embodiments, the anti-CD40 antibody is Y12XX-hz28.

Y12XX-hz28 [Vh-hzl4;Vk-hz2] HCDR1
SYWMH (SEQ ID NO: 179)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] HCDR2
QINPTTGRSQYNEKFKT (SEQ ID NO: 180)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] HCDR3
WGLQPFAY (SEQ ID NO: 181)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] LCDR1
KASQDVSTAVA (SEQ ID NO: 183)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] LCDR2
SASYRYT (SEQ ID NO: 184)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] LCDR3

QQHYSTPWT (SEQ ID NO: 185)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] HCVR
QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQY
NEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS (SEQ ID
NO: 178)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] LCVR
DIQMTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGTKVEIK (SEQ ID NO: 182)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] HC
QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQY
NEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPG (SEQ ID NO: 186)

Y12XX-hz28 [Vh-hzl4;Vk-hz2] LC
DIQMTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVPSRFS
GSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH
KVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 187)

[0818] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 188/190. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified

according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0819] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 179, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185.

[0820] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 188; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 190. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 188. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 190.

[0821] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 191; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 192. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 191. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 192. In some embodiments, the anti-CD40 antibody is Y12XX-hz40.

Y12XX-hz40 [Vh-hzl2;Vk-hz3] HCDR1
SYWMH (SEQ ID NO: 179)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] HCDR2

QINPSQGRSQYNEKFKT (SEQ ID NO: 189)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] HCDR3
WGLQPFAY (SEQ ID NO: 181)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] LCDR1
KASQDVSTAVA (SEQ ID NO: 183)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] LCDR2
SASYRYT (SEQ ID NO: 184)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] LCDR3
QQHYSTPWT (SEQ ID NO: 185)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] HCVR
QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSQGRSQY
NEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS (SEQ ID
NO: 188)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] LCVR
EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSG
SGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIK (SEQ ID NO: 190)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] HC
QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSQGRSQY
NEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPG (SEQ ID NO: 191)

Y12XX-hz40 [Vh-hzl2;Vk-hz3] LC

EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSG
SGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 192)

[0822] In some embodiments, the present disclosure provides monospecific anti-CD40 antibodies or antigen-binding fragments thereof that specifically bind CD40 (e.g., human CD40). In some embodiments, the anti-CD40 antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 178/190. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0823] In some embodiments, the anti-CD40 antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 179, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185.

[0824] In some embodiments, the anti-CD40 antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 178; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 190. In some embodiments, the anti-CD40 antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 178. In some embodiments, the anti-CD40 antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 190.

[0825] In some embodiments, the anti-CD40 antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 186; and/or a light chain comprising an amino acid sequence

that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 192. In some embodiments, the anti-CD40 antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 186. In some embodiments, the anti-CD40 antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 192. In some embodiments, the anti-CD40 antibody is Y12XX-hz42.

Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCDR1
SYWMH (SEQ ID NO: 179)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCDR2
QINPTTGRSQYNEKFKT (SEQ ID NO: 180)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCDR3
WGLQPFAY (SEQ ID NO: 181)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCDR1
KASQDVSTAVA (SEQ ID NO: 183)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCDR2
SASYRYT (SEQ ID NO: 184)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCDR3
QQHYSTPWT (SEQ ID NO: 185)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCVR
QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQY NEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS (SEQ ID NO: 178)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCVR
EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSG SGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIK (SEQ ID NO: 190)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] HC
QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQY
NEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSSASTKGP
SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD
IAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ
KSLSLSPG (SEQ ID NO: 186)

Y12XX-hz42 [Vh-hzl4;Vk-hz3] LC
EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSG
SGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSG
TASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKV
YACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 192)

[0826] In some cases, the antibody comprises a human IgG heavy chain constant region. In some cases, the human IgG heavy chain constant region is isotype IgG1. In some cases, the human IgG heavy chain constant region is isotype IgG4.

CD40xCD40 Bispecific Antigen-Binding Molecules

[0827] The present disclosure also provides multispecific antigen-binding molecules that specifically bind CD40. In some embodiments, the bispecific antigen-binding molecule comprises two CD40 binding arms comprising distinct HCVRs paired with a common LCVR. In some embodiments, the bispecific antigen-binding molecule comprises two CD40 binding arms comprising distinct HCVRs which are not paired with a common LCVR but instead are paired with distinct LCVRs which can comprise, e.g., without limitation any of the LCVRs, or combination thereof, disclosed herein. In some embodiments, the antigen-binding molecule is a bispecific antigen-binding molecule, e.g., bispecific antibody. Any of the anti-CD40 antibodies disclosed herein can be in bispecific configuration, including a second arm derived from any other anti-CD40 antibody disclosed herein. In some embodiments, the bispecific antigen-binding molecule comprises a first antigen-binding domain (D1) that binds a first epitope of CD40 (e.g., human CD40), and a second antigen-binding domain (D2) that binds a second epitope of CD40

(e.g., human CD40). In some embodiments, D1 and D2 do not compete with one another for binding to CD40 (e.g., human CD40). In some embodiments, D1 and D2 compete with one another for binding to CD40 (e.g., human CD40).

[0828] In some embodiments, the bispecific antigen-binding molecule comprises two different heavy chain immunoglobulin variable regions, wherein at least one heavy chain immunoglobulin variable region comprises an HCDR1-HCDR2-HCDR3 amino acid sequences set contained within an HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, and 188. In some embodiments, the bispecific antigen-binding molecule comprises two different heavy chain immunoglobulin variable regions, wherein at least one heavy chain immunoglobulin variable region comprises an HCDR1-HCDR2-HCDR3 amino acid sequences set contained within an HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, and 32. In some embodiments, each heavy chain immunoglobulin variable region comprises an HCDR1-HCDR2-HCDR3 amino acid sequences set contained within an HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, and 188. In some embodiments, each heavy chain immunoglobulin variable region comprises an HCDR1-HCDR2-HCDR3 amino acid sequences set contained within an HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 22, and 32. In some embodiments, the CDRs within the HCVR are identified according to the Kabat definition. In some embodiments, the CDRs are identified according to the Chothia definition. In some embodiments, the CDRs are identified according to the AbM definition. In some embodiments, the CDRs are identified according to the IMGT definition.

[0829] In some embodiments, at least one heavy chain immunoglobulin variable region comprises an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 2, 22, 32, 57, 67, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 77, 163, 176, 178, or 188. In some embodiments, at least one heavy chain immunoglobulin variable region comprises or consists of the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188.

[0830] In some embodiments, one or more of the heavy chain immunoglobulin variable regions comprises a set of HCDR sequences selected from the group consisting of:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8;

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28; and

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38.

[0831] In some embodiments, the bispecific antigen-binding molecule comprises (i) an antigen-binding domain that comprises a heavy chain immunoglobulin variable region comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8; and (ii) an antigen-binding domain that comprises a heavy chain immunoglobulin variable region comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28.

[0832] In some embodiments, the bispecific antigen-binding molecule comprises (i) an antigen-binding domain that comprises a heavy chain immunoglobulin variable region comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8; and (ii) an antigen-binding domain that comprises a heavy chain immunoglobulin variable region comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38.

[0833] In some embodiments, the bispecific antigen-binding molecule comprises (i) an antigen-binding domain that comprises a heavy chain immunoglobulin variable region comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28; and (ii) an antigen-binding domain that comprises a heavy chain immunoglobulin variable region comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38.

[0834] In some embodiments, the bispecific antigen-binding molecule comprises a common light chain variable region. In some embodiments, the light chain variable region comprises an LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the LCVR amino acid sequence of SEQ ID NO: 10. In some embodiments, the light chain variable region comprises an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0835] In some embodiments, the bispecific antigen-binding molecule comprises a D1 that binds a first epitope of human CD40, wherein the D1 domain comprises a heavy chain immunoglobulin chain comprising:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28.

[0836] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the D1 domain comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 4, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 6, and an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 8. In some embodiments, the D1 domain comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 2. In some embodiments, the D1 domain comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 2.

[0837] In some embodiments, the D1 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 46. In some embodiments, the D1 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 46.

[0838] In some embodiments, the D1 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at

least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 52. In some embodiments, the D1 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 52.

[0839] In some embodiments, the D1 domain further comprises a light chain immunoglobulin chain comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0840] In some embodiments, the D1 domain comprises a LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0841] In some embodiments, the D1 domain comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the D1 domain comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0842] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28. In some embodiments, the D1 domain comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 24, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 26, and an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 28. In some embodiments, the D1 domain comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 22. In some embodiments, the D1 domain comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 22.

[0843] In some embodiments, the D1 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 42. In some embodiments, the D1 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 42.

[0844] In some embodiments, the D1 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 48. In some embodiments, the D1 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 48.

[0845] In some embodiments, the D1 domain further comprises a light chain immunoglobulin chain comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0846] In some embodiments, the D1 domain comprises a LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0847] In some embodiments, the D1 domain comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the D1 domain comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0848] In some embodiments, the bispecific antigen-binding molecule comprises a D2 that binds a second epitope of human CD40, wherein the D2 domain comprises a heavy chain immunoglobulin chain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38. In some embodiments, the D2 domain comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 34, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 36, and an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 38. In some embodiments, the D2 domain comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 32. In some embodiments, the D2 domain comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 32.

[0849] In some embodiments, the D2 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence

identity to SEQ ID NO: 44. In some embodiments, the D2 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 44.

[0850] In some embodiments, the D2 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 50. In some embodiments, the D2 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 50.

[0851] In some embodiments, the D2 domain further comprises a light chain immunoglobulin chain comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0852] In some embodiments, the D2 domain comprises an LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0853] In some embodiments, the D2 domain comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the D2 domain comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0854] In some embodiments, the bispecific antigen-binding molecule comprises a D1 domain that binds a first epitope of human CD40 and a D2 domain that binds a second epitope of human CD40, wherein the D1 domain comprises a heavy chain immunoglobulin chain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38. In some embodiments, the D1 domain comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 34, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 36, and an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 38. In some embodiments, the D1 domain comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 32. In some embodiments, the D1 domain comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 32.

[0855] In some embodiments, the D1 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 205. In some embodiments, the D1 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 205.

[0856] In some embodiments, the D2 domain comprises a heavy chain immunoglobulin chain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8. In some embodiments, the D2 domain comprises an HCDR1 consisting of the amino acid sequence of SEQ ID NO: 4, an HCDR2 consisting of the amino acid sequence of SEQ ID NO: 6, and an HCDR3 consisting of the amino acid sequence of SEQ ID NO: 8. In some embodiments, the D2 domain comprises an HCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 2. In some embodiments, the D2 domain comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 2.

[0857] In some embodiments, the D2 domain comprises a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 207. In some embodiments, the D2 domain comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 207.

[0858] In some embodiments, the D1 and/or D2 domain further comprises a light chain immunoglobulin chain comprising an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the D1 and/or D2 domain comprises a LCVR comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 10. In some embodiments, the D1 and/or D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the D1 and/or D2 domain comprises a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 20. In some embodiments, the D1 and/or D2 domain comprises a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0859] In some embodiments, the bispecific antigen-binding molecule comprises:

a D1 domain that binds a first epitope of human CD40, wherein the D1 domain comprises an immunoglobulin chain comprising an HCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 16; and

a D2 domain that binds a second epitope of human CD40, wherein the D2 domain comprises an immunoglobulin chain comprising an HCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 16.

[0860] In some embodiments, the bispecific antigen-binding molecule comprises:

a D1 domain that comprises an HCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 2, and an LCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 10; and

a D2 domain that comprises an HCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 32, and an LCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 10.

[0861] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10; and a D2 domain that comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

[0862] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 46 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20; and a D2 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 44 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0863] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 52 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20; and a D2 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 50 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0864] In some embodiments, the bispecific antigen-binding molecule comprises:

a D1 domain that binds a first epitope of human CD40, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 16; and

a D2 domain that binds a second epitope of human CD40, wherein the D2 domain comprises an HCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 16.

[0865] In some embodiments, the bispecific antigen-binding molecule comprises:

a D1 domain that comprises an HCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 22, and an LCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 10; and

a D2 domain that comprises an HCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 32, and an LCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 10.

[0866] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 22 and an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10; and a D2 domain that comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

[0867] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 42 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20; and a D2 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 44 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0868] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 48 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20; and a D2 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 50 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0869] In some embodiments, the bispecific antigen-binding molecule comprises:

a D1 domain that binds a first epitope of human CD40, wherein the D1 domain comprises an immunoglobulin chain comprising an HCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 16; and

a D2 domain that binds a second epitope of human CD40, wherein the D2 domain comprises an immunoglobulin chain comprising an HCDR1 comprising or consisting of the

amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising or consisting of the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising or consisting of the amino acid sequence of SEQ ID NO: 16.

[0870] In some embodiments, the bispecific antigen-binding molecule comprises:

a D1 domain that comprises an HCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 32, and an LCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 10; and

a D2 domain that comprises an HCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 2, and an LCVR comprising an amino acid sequence that has at least 85% (e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99%) sequence identity to SEQ ID NO: 10.

[0871] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10; and a D2 domain that comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 10.

[0872] In some embodiments, the bispecific antigen-binding molecule comprises: a D1 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 205 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20; and a D2 domain that comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 207 and a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 20.

[0873] The bispecific antigen-binding molecules disclosed herein may be bispecific antibodies. In some cases, the bispecific antibody comprises a human IgG heavy chain constant region. In some cases, the human IgG heavy chain constant region is isotype IgG1. In some cases, the human IgG heavy chain constant region is isotype IgG4.

[0874] The first antigen-binding domain and the second antigen-binding domain may be directly or indirectly connected to one another to form a bispecific antigen-binding molecule of the present invention. Alternatively, the first antigen-binding domain and the second antigen-binding domain may each be connected to a separate multimerizing domain. The association of one multimerizing domain with another multimerizing domain facilitates the association between the two antigen-binding domains, thereby forming a bispecific antigen-binding molecule. As used herein, a "multimerizing domain" is any macromolecule, protein, polypeptide, peptide, or amino acid that has the ability to associate with a second multimerizing domain of the same or similar structure or constitution. For example, a multimerizing domain may be a polypeptide comprising an immunoglobulin CH3 domain. A non-limiting example of a multimerizing component is an Fc portion of an immunoglobulin (comprising a CH2-CH3 domain), e.g., an Fc domain of an IgG selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group.

[0875] In some embodiments, a bispecific antigen-binding molecules of the present disclosure comprises two multimerizing domains, e.g., two Fc domains that are each individually part of a separate antibody heavy chain. The first and second multimerizing domains may be of the same IgG isotype such as, e.g., IgG1/IgG1, IgG2/IgG2, IgG4/IgG4. Alternatively, the first and second multimerizing domains may be of different IgG isotypes such as, e.g., IgG1/IgG2, IgG1/IgG4, IgG2/IgG4, etc.

[0876] In some embodiments, the multimerizing domain is an Fc fragment or an amino acid sequence of from 1 to about 200 amino acids in length containing at least one cysteine residue. In other embodiments, the multimerizing domain is a cysteine residue, or a short cysteine-containing peptide. Other multimerizing domains include peptides or polypeptides comprising or consisting of a leucine zipper, a helix-loop motif, or a coiled-coil motif.

[0877] In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody that has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to REGN16334. In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody having the amino acid sequences of REGN16334.

[0878] In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody that has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or

at least 99% sequence identity, to REGN16335. In some embodiments, the bispecific antigen-binding molecule is a bispecific antibody having the amino acid sequences of REGN16335.

[0879] In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody that has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to REGN16431. In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody having the amino acid sequences of REGN16431.

[0880] In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody that has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to REGN16432. In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody having the amino acid sequences of REGN16432.

[0881] In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody that has at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to REGN20484. In some embodiments, the bispecific antigen-binding molecule is an anti-CD40xCD40 bispecific antibody having the amino acid sequences of REGN20484.

Sequence Variants

[0882] The antigen-binding molecules of the present disclosure may comprise one or more amino acid substitutions, insertions, and/or deletions in the framework and/or CDR regions of the heavy and/or light chain variable domains as compared to the corresponding germline sequences from which the individual antigen-binding domains were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germ line sequences available from, for example, public antibody sequence databases. The antigen-binding molecules of the present disclosure may comprise antigen binding fragments which are derived from any of the exemplary amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to

herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antigen-binding domain was originally derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence *(i.e.,* a germline sequence that is different from the germ line sequence from which the antigen-binding domain was originally derived). Furthermore, the antigen-binding domains may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germ line sequence while certain other residues that differ from the original germ line sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antigen-binding domains that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties, reduced immunogenicity, etc. Bispecific antigen-binding molecules comprising one or more antigen-binding domains obtained in this general manner are encompassed within the present disclosure.

[0883] The present disclosure also includes antigen-binding molecules wherein one or both antigen-binding domains comprise variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present disclosure includes antigen-binding molecules comprising an antigen-binding domain having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 conservative amino acid substitution(s) relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic

side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate; and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443-1445. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[0884] The present disclosure also includes antigen-binding molecules comprising an antigen binding domain with an HCVR, LCVR, and/or CDR amino acid sequence that is substantially identical to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. In some embodiments, an antigen-binding molecule comprises HCVR, LCVR, and/or CDR amino acid sequence having at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to a sequence disclosed in **Table 41**. In some embodiments, an antigen-binding molecule comprises HCVR, LCVR, and/or CDR amino acid sequence having at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to a sequence disclosed in **Table 41**, wherein the differences in the amino acid residue(s) relative to the sequence disclosed in **Table 41** are conservative substitutions or moderately conservative substitutions.

Antigen-Binding Proteins Comprising Fc Modifications

[0885] In some embodiments, a CD40 antigen-binding molecule as disclosed herein (e.g., a CD40xCD40 bispecific antigen-binding molecule, e.g., as disclosed in any one of **Tables 3-6**) comprises an Fc domain comprising one or more modifications or mutations that enhance or diminish antibody binding to the FcRn receptor. For example, the present disclosure includes antigen-binding molecules comprising one or more mutations in the CH2 and/or CH3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal.

[0886] Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P). See, e.g., Ko et al., *BioDrugs* 2021, 35:147-157.

[0887] In certain embodiments, a CD40xCD40 bispecific antigen-binding molecule comprises an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (*e.g.,* T250Q and M248L); 252Y, 254T and 256E (*e.g.,* M252Y, S254T and T256E); 428L and 434S (*e.g.,* M428L and N434S); and 433K and 434F (*e.g.,* H433K and N434F).

[0888] In some embodiments, the CD40xCD40 bispecific antigen-binding molecules of the present disclosure comprise a modified Fc domain having reduced effector function. As used herein, a "modified Fc domain having reduced effector function" means any Fc portion of an immunoglobulin that has been modified, mutated, truncated, etc., relative to a wild-type, naturally occurring Fc domain such that a molecule comprising the modified Fc exhibits a reduction in the severity or extent of at least one effect selected from the group consisting of cell killing (e.g., ADCC and/or CDC), complement activation, phagocytosis and opsonization, relative to a comparator molecule comprising the wild-type, naturally occurring version of the Fc portion. In certain embodiments, a "modified Fc domain having reduced effector function" is an Fc domain with reduced or attenuated binding to an Fc receptor (e.g., FcγR).

[0889] In certain embodiments, a modified Fc domain having reduced binding to an Fc receptor (e.g., Fcγ receptor, e.g., FcγRI, FcγRIIA, FcγRIIB, or FcγRIIIA) is a variant IgG1 Fc or a variant IgG4 Fc comprising one or more substitutions or modifications in the hinge region and/or a CH region (e.g., CH2). For example, a modified Fc domain may comprise a variant IgG1 Fc wherein at least one amino acid of an IgG1 Fc hinge region and/or CH region is replaced with the corresponding amino acid from an IgG2 Fc hinge region and/or CH region. In one example, the variant IgG1 Fc can comprise a human IgG2 lower hinge amino acid sequence or can comprise both a human IgG2 lower hinge amino acid sequence and a human IgG4 CH2 amino acid sequence. For example, in some embodiments, the heavy chain constant region can

comprise a variant IgG1 Fc in which positions 233-236 by EU numbering are occupied by PVA. See, e.g., US 10,988,537, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the heavy chain constant region can comprise a variant IgG1 Fc in which the IgG1 CH2 region is replaced with the corresponding amino acids from the IgG4 CH2 region and in which positions 233-236 by EU numbering are occupied by PVA. Alternatively, a modified Fc domain may comprise a variant IgG4 Fc wherein at least one amino acid of an IgG4 Fc hinge region and/or CH region is replaced with the corresponding amino acid from an IgG2 Fc hinge region and/or CH region. In one example, the variant IgG4 Fc can comprise a human IgG2 lower hinge amino acid sequence. For example, in some embodiments, the heavy chain constant region can comprise a variant IgG4 Fc in which positions 233-236 by EU numbering are occupied by PVA. See, e.g., US 10,988,537, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, a modified Fc domain comprises modifications in which each of positions 233-236 by EU numbering is occupied by G or is unoccupied. For example, in some embodiments, a modified Fc domain can comprise a modified hinge region in which positions 233-236 by EU numbering are occupied by GGG. See, e.g., US 11,518,807, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the heavy chain constant region can comprise a variant IgG1 Fc in which the IgG1 CH2 region is replaced with the corresponding amino acids from the IgG4 CH2 region and in which positions 233-236 by EU numbering are occupied by GGG. Non-limiting, exemplary modified Fc regions that can be used in the context of the present disclosure are set forth in US Patent No. 11,518,807, the disclosure of which is hereby incorporated by reference in its entirety, as well as any functionally equivalent variants of the modified Fc regions set forth therein. Other modified Fc domains and Fc modifications that can be used in the context of the present disclosure include any of the modifications as set forth in US 8,697,396, US 10,988,537, US 2014/0171623, US 2014/0134162, US 2014/0243504, and WO 2014/043361, the disclosures of each of which are incorporated by reference herein.

[0890] In certain embodiments, a bispecific antigen-binding molecule as disclosed herein comprises immunoglobulin heavy chains that are heterodimeric (i.e., differing by at least one amino acid) and have differential affinity toward an affinity reagent, such as Protein A. In some embodiments, one of the heavy chains comprises one or more modifications in the Fc domain that reduces or eliminates binding of the Fc domain to Protein A. In some embodiments, one of the heavy chains comprises H435R/Y436F (by EU numbering system) substitutions in the CH3 region. Non-limiting, exemplary modified Fc regions that can be used in the context of the

present disclosure are set forth in US Patent No. 8,586,713, the disclosure of which is hereby incorporated by reference in its entirety.

[0891] All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present disclosure.

Polynucleotides, Vectors, and Host Cells

[0892] In another aspect, the present disclosure provides nucleic acid molecules comprising one or more polynucleotide sequences encoding the antigen-binding molecules disclosed herein, as well as vectors (e.g., expression vectors) encoding such polynucleotide sequences and host cells into which such vectors have been introduced.

[0893] Polynucleotides, as disclosed herein, may encode all or a portion of an antigen-binding molecule, antibody, or antigen-binding fragment as disclosed throughout the present disclosure. In some cases, a single polynucleotide may encode both a HCVR and a LCVR (e.g., defined with reference to the CDRs contained within the respective amino acid sequence-defined HCVR and LCVR, defined with reference to the amino acid sequences of the CDRs of the HCVR and LCVR, respectively, or defined with reference to the amino acid sequences of the HCVR and LCVR, respectively) of an antibody or antigen-binding fragment, or the HCVR and LCVR may be encoded by separate polynucleotides (i.e., a pair of polynucleotides). In the latter case, in which the HCVR and LCVR are encoded by separate polynucleotides, the polynucleotides may be combined in a single vector or may be contained in separate vectors (i.e., a pair of vectors). In any case, a host cell used to express the polynucleotide(s) or vector(s) may contain the full complement of component parts to generate the antibody or antigen-binding fragment thereof. For example, a host cell may comprise separate vectors, each encoding a HCVR and a LCVR, respectively, of an antibody or antigen-binding fragment thereof as discussed above or herein. Similarly, the polynucleotide or polynucleotides, and the vector or vectors, may be used to express the full-length heavy chain and full-length light chain of an antibody as discussed above or herein. For example, a host cell may comprise a single vector with polynucleotides encoding both a heavy chain and a light chain of an antibody, or the host cell may comprise separate vectors with polynucleotides encoding, respectively, a heavy chain and a light chain of an antibody as disclosed above or herein.

[0894] In some embodiments, the nucleic acid molecule comprises one or more polynucleotide sequences encoding an antigen-binding molecule disclosed in any of **Tables 3**-

6. In some embodiments, the nucleic acid molecule comprises one or more polynucleotide sequences set forth in **Table 41**.

[0895] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an CD40 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 4, 6, and 8, respectively, of SEQ ID NOs: 24, 26, and 28, respectively, or of SEQ ID NOs: 34, 36, and 38, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an CD40 HCVR comprising or consisting of the sequence of SEQ ID NO: 2, SEQ ID NO: 22, or SEQ ID NO: 32.

[0896] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising or consisting of the sequence of SEQ ID NO: 10.

[0897] In some embodiments, compositions are provided comprising one or more nucleic acid molecules as disclosed herein. For example, in some embodiments, a composition comprises a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR and/or LCVR of a first antigen-binding molecule that binds a first epitope of CD40, and a second nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR and/or LCVR of a second antigen-binding molecule that binds a second epitope of CD40. In some embodiments, a composition comprises a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of a first antigen-binding molecule that binds a first epitope of CD40, a second nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of a first antigen-binding molecule that binds a first epitope of CD40, a third nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of a second antigen-binding molecule that binds a second epitope of CD40, and a fourth nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of a second antigen-binding molecule that binds a second epitope of CD40. In some embodiments, the HCVR sequences of the first and second antigen-binding molecules are selected from: an CD40 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 4, 6, and 8, respectively, an CD40 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 24, 26, and 28, respectively, and an CD40 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 34, 36, and 38, respectively. In some embodiments, the HCVR sequences of the first and second antigen-binding molecules are selected from SEQ ID NO: 2, SEQ ID NO: 22, and SEQ ID NO: 32. In

some embodiments, the LCVR sequences of first and second antigen-binding molecules each comprise an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the LCVR sequences of first and second antigen-binding molecules each comprise the sequence of SEQ ID NO: 10.

[0898] In another aspect, the present disclosure also provides recombinant expression vectors carrying one or more nucleic acid molecules as disclosed herein, as well as host cells into which such vectors have been introduced. In some embodiments, the host cell is a prokaryotic cell (e.g., *E. coli*). In some embodiments, the host cell is a eukaryotic cell, such as a non-human mammalian cell (e.g., a Chinese Hamster Ovary (CHO) cell). Also provided herein are methods of producing the antigen-binding molecules of the disclosure by culturing the host cells under conditions permitting production of the antigen-binding molecules, and recovering the antigen-binding molecules so produced.

Characterization of CD40xCD40 Bispecific Antigen-Binding Molecules

[0899] The present disclosure includes antibodies and antigen-binding fragments thereof that bind to human CD40 with high affinity, e.g., bispecific antigen-binding molecules that bind to two different epitopes of CD40. In some embodiments, the antibodies and antigen binding fragments thereof (e.g., bispecific antigen-binding molecules) bind to CD40 and inhibit CD40L-induced activation but do not have agonist activity and/or cytotoxic effector functions.

[0900] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein, such as a bispecific antibody having the amino acid sequences of REGN16334, REGN16335, REGN16431, REGN16432, or REGN20484) that bind human CD40 (e.g., at 25°C or 37°C) with a K_D of less than about 75 nM as measured by surface plasmon resonance, *e.g.,* using an assay format as described in Example 2 herein. In certain embodiments, the antigen-binding molecules of the present disclosure bind human CD40 with a K_D of less than about 75 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 500 pM, less than about 400 pM, less than about 300 pM, less than about 200 pM, less than about 100 pM, less than about 90 pM, less than about 80 pM, less than about 70 pM, less than about 60 pM, less than about 50 pM, less than about 40 pM, less than about 30 pM, less than about 20 pM, less than about 10 pM, less than about 5 pM, less than about 4 pM, less than about 2 pM, less than about 1 pM, less

than about 0.5 pM, less than about 0.2 pM, less than about 0.1 pM, or less than about 0.05 pM, as measured by surface plasmon resonance, e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay.

[0901] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein, such as a bispecific antibody having the amino acid sequences of REGN16334, REGN16335, REGN16431, REGN16432, or REGN20484) having an improved half-life as compared to monospecific antibodies (e.g., parental CD40 antibodies). In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein) that bind human CD40 with a dissociative half-life ($t_{½}$) of greater than about 70 minutes as measured by surface plasmon resonance at 25°C, e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments of the present disclosure bind human CD40 with a $t_{½}$ of greater than about 75 minutes, greater than about 80 minutes, greater than about 85 minutes, or greater than about 90 minutes, as measured by surface plasmon resonance at 25°C, e.g., using an assay format as defined in Example 2 herein, or a substantially similar assay.

[0902] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein, such as a bispecific antibody having the amino acid sequences of REGN16334, REGN16335, REGN16431, REGN16432, or REGN20484) that inhibit binding of human CD40 (e.g., a monomeric form of hCD40) to human CD40L. In some embodiments, inhibition of CD40 binding to CD40L is measured using an ELISA-based blocking assay as described in Example 4 herein. In some embodiments, a bispecific antigen-binding molecule inhibits binding of human CD40 (e.g., hCD40 monomer) to human CD40L by at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, or more, e.g., using an assay format as defined in Example 4 herein, or a substantially similar assay.

[0903] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein, such as a bispecific antibody having the amino acid sequences of REGN16334, REGN16335, REGN16431, REGN16432, or REGN20484) that specifically interact (e.g., bind with) cells that express CD40. The extent to which an antigen-binding molecule binds cells that express CD40 can be assessed by flow cytometry, as illustrated in Example 5 below. For example, in some embodiments, the present disclosure provides anti-CD40xCD40 bispecific antibodies that specifically bind cells that express CD40 on the cell surface (e.g., primary human B cells, or a human B cell line such as

Ramos 2G6.4C10). In some embodiments, the disclosure provides anti-CD40xCD40 bispecific antibodies that bind CD40-expressing cells or cell lines with an EC_{50} value of about 10 nM or less, e.g., from about 0.5 nM to about 10 nM, e.g., an EC_{50} value of about 1 nM, about 1.5 nM, about 2 nM, about 2.5 nM, about 3 nM, about 3.5 nM, about 4 nM, about 4.5 nM, about 5 nM, about 5.5 nM, about 6 nM, about 6.5 nM, about 7 nM, about 7.5 nM, about 8 nM, about 8.5 nM, about 9 nM, about 9.5 nM, or about 10 nM, as determined by flow cytometry as set forth in Example 5 or a substantially similar assay.

[0904] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein, such as a bispecific antibody having the amino acid sequences of REGN16334, REGN16335, REGN16431, REGN16432, or REGN20484) that inhibit CD40L-induced activation. In some embodiments, CD40L-induced activation is measured using a reporter assay, such as a luciferase-based reporter assay that quantitatively assesses receptor activation in a CD40-expressing cell by measuring downstream gene expression. In some embodiments, the reporter assay is an assay described in Example 6 herein. In some embodiments, CD40L-induced activation is measured by a cytokine secretion assay (e.g., secretion of IL-6, IL-10, IL-23, or TNFα) in the presence of CD40L. In some embodiments, the cytokine secretion assay is performed in primary cells that express CD40 (e.g., human B cells). In some embodiments, the cytokine secretion assay is performed in a stable cell line, e.g., a cell line that expresses CD40 and a reporter gene such as luciferase. In some embodiments, the cytokine secretion assay is an assay described in Example 7 herein. In some embodiments, the anti-CD40xCD40 bispecific antibody inhibits CD40L-induced activation (e.g., reporter gene expression or cytokine secretion) by at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90% or more, relative to a control or a reference value.

[0905] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein, such as a bispecific antibody having the amino acid sequences of REGN16334, REGN16335, REGN16431, REGN16432, or REGN20484) that do not significantly agonize CD40 in the absence of CD40L. As used herein, "do[es] not significantly agonize CD40 in the absence of CD40L" means that in the presence of the bispecific antigen-binding molecule and absence of CD40L, the level of activation of CD40 is less than 15%, e.g., less than 13%, less than 10%, less than 8%, or less than 6%, e.g., as measured by downstream gene expression or cytokine secretion. In some embodiments, agonism of CD40 is measured by a reporter assay, such as a luciferase-based reporter assay that quantitatively assesses receptor activation in a CD40-expressing cell by measuring

downstream gene expression. In some embodiments, agonism of CD40 is measured by a cytokine secretion assay (e.g., secretion of IL-6, IL-10, IL-23, or TNFα) in the absence of CD40L. In some embodiments, the assay is an assay described in Example 6 or Example 8 herein.

Epitope Mapping and Related Technologies

[0906] In some embodiments, the epitope on CD40 to which the antigen-binding molecules of the present disclosure bind (e.g., a first epitope of human CD40 to which a first antigen-binding domain (D1) binds, or a second epitope of human CD40 to which a second antigen-binding domain (D2) binds) may consist of a single contiguous sequence of 3 or more *(e.g.,* 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids of a CD40 protein. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) of CD40. The term "epitope," as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0907] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antigen-binding domain of an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques that can be used to determine an epitope or binding domain of a particular antibody or antigen-binding domain include, e.g., routine crossblocking assay such as that described in *Antibodies*, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY), point mutagenesis (e.g., alanine scanning mutagenesis, arginine scanning mutagenesis, *etc.*), peptide blots analysis (Reineke, 2004, *Methods Mol Biol* 248:443-463), protease protection, and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, *Protein Science* 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to

the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem. 73*:256A-265A. X-ray crystal structure analysis can also be used to identify the amino acids within a polypeptide with which an antibody interacts.

[0908] In some embodiments, the present disclosure includes anti-CD40 antibodies and anti-CD40xCD40 bispecific antibodies that bind to the same epitope or epitopes as any of the specific exemplary antibodies described herein (e.g., antibodies comprising any of the amino acid sequences set forth in **Table 41** below). In some embodiments, the present disclosure includes anti-CD40 antibodies and anti-CD40xCD40 bispecific antibodies that compete for binding with the exemplary antibodies described herein (e.g., antibodies comprising any of the amino acid sequences set forth in **Table 41** below).

[0909] In some embodiments, the present disclosure provides anti-CD40xCD40 bispecific antibodies comprising a first antigen-binding domain (D1) that binds a first epitope of human CD40 and a second antigen-binding domain (D1) that binds a second epitope of human CD40, wherein the first epitope and the second epitope are different epitopes of CD40. In some embodiments, the first epitope and the second epitope are non-overlapping epitopes.

[0910] In some embodiments, the present disclosure provides anti-CD40xCD40 bispecific antibodies comprising a first antigen-binding domain (D1) that binds a first epitope of human CD40 and a second antigen-binding domain (D1) that binds a second epitope of human CD40, wherein D1 and D2 do not compete with one another for binding to human CD40.

[0911] One skilled in the art can determine whether or not a particular antigen-binding molecule (e.g., antibody) or antigen-binding domain thereof binds to the same epitope as, or competes for binding with, a reference antigen-binding molecule of the present disclosure by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope on CD40 as a reference bispecific antigen-binding molecule of the present disclosure, the reference bispecific molecule is first allowed to bind to a CD40 protein. Next, the ability of a test antibody to bind to the CD40 molecule is assessed. If the test antibody is able to bind to CD40 following saturation binding with the reference bispecific antigen-binding molecule, it can be concluded that the test antibody binds to a different epitope of CD40 than the reference bispecific antigen-binding molecule. On the other hand, if the test antibody is not able

to bind to the CD40 molecule following saturation binding with the reference bispecific antigen-binding molecule, then the test antibody may bind to the same epitope of CD40 as the epitope bound by the reference bispecific antigen-binding molecule of the disclosure. Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference bispecific antigen-binding molecule or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present disclosure, two antigen-binding proteins bind to the same (or overlapping) epitope if, e.g., a 1-, 2-, 5-, 10-, 20- or 100-fold excess of one antigen-binding protein inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., *Cancer Res*. 1990:50:1495-1502). Alternatively, two antigen-binding proteins are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antigen-binding protein reduce or eliminate binding of the other. Two antigen-binding proteins are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antigen-binding protein reduce or eliminate binding of the other.

[0912] To determine if an antibody or antigen-binding domain thereof competes for binding with a reference antigen-binding molecule, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antigen-binding molecule is allowed to bind to a CD40 protein under saturating conditions followed by assessment of binding of the test antibody to the CD40 molecule. In a second orientation, the test antibody is allowed to bind to a CD40 molecule under saturating conditions followed by assessment of binding of the reference antigen-binding molecule to the CD40 molecule. If, in both orientations, only the first (saturating) antigen-binding molecule is capable of binding to the CD40 molecule, then it is concluded that the test antibody and the reference antigen-binding molecule compete for binding to CD40. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antigen-binding molecule may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Preparation of Antigen-Binding Domains and Construction of Multispecific Antigen-Binding Molecules

[0913] Antigen-binding domains specific for particular antigens can be prepared by any antibody generating technology known in the art. Once obtained, two different antigen-binding domains can be appropriately arranged relative to one another to produce a bispecific antigen-binding molecule of the present disclosure using routine methods. (A discussion of exemplary bispecific antibody formats that can be used to construct the bispecific antigen-binding molecules of the present disclosure is provided elsewhere herein). In certain embodiments, one or more of the individual components (e.g., heavy and light chains) of the multispecific antigen-binding molecules are derived from chimeric, humanized or fully human antibodies. Methods for making such antibodies are well known in the art. For example, one or more of the heavy and/or light chains of the bispecific antigen-binding molecules of the present disclosure can be prepared using VELOCIMMUNE™ technology. Using VELOCIMMUNE™ technology (or any other human antibody generating technology), high affinity chimeric antibodies to a particular antigen (e.g., CD40) are initially isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate fully human heavy and/or light chains that can be incorporated into the bispecific antigen-binding molecules.

[0914] In some embodiments, genetically engineered animals may be used to make human bispecific antigen binding molecules. For example, a genetically modified mouse can be used which is incapable of rearranging and expressing an endogenous mouse immunoglobulin light chain variable sequence, wherein the mouse expresses only one or two human light chain variable domains encoded by human immunoglobulin sequences operably linked to the mouse kappa constant gene at the endogenous mouse kappa locus. Such genetically modified mice can be used to produce fully human bispecific antigen-binding molecules comprising two different heavy chains that associate with an identical light chain that comprises a variable domain derived from one of two different human light chain variable region gene segments. (See, e.g., US 2011/0195454, the entire contents of which are incorporated herein by reference, for a detailed discussion of such engineered mice and the use thereof to produce bispecific antigen-binding molecules). As used herein, "fully human" refers to an antigen-binding molecule, e.g., an antibody, or antigen-binding fragment or immunoglobulin domain thereof, comprising an amino acid sequence encoded by a DNA derived from a human sequence over the entire length of each polypeptide of the antigen-binding molecule, antibody, antigen-binding

fragment, or immunoglobulin domain thereof. In some instances, the fully human sequence is derived from a protein endogenous to a human. In other instances, the fully human protein or protein sequence comprises a chimeric sequence wherein each component sequence is derived from human sequence. While not being bound by any one theory, chimeric proteins or chimeric sequences are generally designed to minimize the creation of immunogenic epitopes in the junctions of component sequences, e.g., compared to any wild-type human immunoglobulin regions or domains.

Bioequivalents

[0915] The present disclosure encompasses antigen-binding molecules having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind CD40. Such variant molecules comprise one or more additions, deletions, or substitutions of amino acids when compared to the parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antigen-binding molecules. Likewise, the nucleic acid sequences encoding the antigen-binding molecules of the present disclosure encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antigen binding molecule that is essentially bioequivalent to the antigen-binding molecules disclosed herein.

[0916] The present disclosure includes antigen-binding molecules that are bioequivalent to any of the exemplary antigen-binding molecules set forth herein. Two antigen-binding proteins, e.g., bispecific antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[0917] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[0918] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the first antigen-binding protein (e.g., reference product) and the second antigen-binding protein (e.g., biological product) without an expected increase in

the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[0919] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[0920] Bioequivalence may be demonstrated by *in vivo* and *in vitro* methods. Non-limiting examples of bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[0921] Bioequivalent variants of the exemplary bispecific antigen-binding molecules set forth herein may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other embodiments, bioequivalent antibodies may include the exemplary bispecific antigen-binding molecules set forth herein comprising amino acid changes which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation.

Other CD40 inhibitors

[0922] Other CD40 inhibitors can be used in place of the CD40 antigen-binding molecules disclosed herein in any of the compositions, combinations, kits, or methods disclosed here. A CD40 inhibitor suitable for use in accordance with any of the methods described herein can comprise, without limitation, any of various CD40 antigen-binding molecules described herein, for example, anti-CD40 antibodies, or functional fragments thereof, including monospecific anti-CD40 antibodies, bispecific anti-CD40 antibodies, or multispecific anti-CD40 antibodies, or functional fragments thereof. In some embodiments, a CD40 inhibitor can comprise an CD40 antigen-binding molecule as disclosed herein. However, other CD40 inhibitors can also be used.

[0923] In some embodiments, a CD40 inhibitor may comprise daclizumab.

[0924] In some embodiments, a CD40 inhibitor may comprise, e.g., another CD40-CD40L inhibitor (e.g., an anti-CD40 antibody such as iscalimab [CFZ-533], belselumab [ASKP1240 or 341G2], BI 655064, ch5D12, abiprubart [KPL-404], lucatumumab [HCD122 or CHIR12.12], ravagalimab [ABBV-323], CHIR-5.9, 201A3, BIIB063, Ab101, Ab102, PG102, Antibody A, Antibody B, Antibody C, G28.5, h2C10, BMS3h-37, BMS3h-38, BMS3h-56, BMS3h-198, Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3], Y12XX-hz42 [Vh-hzl4;Vk-hz3], V19, 5C8, 6H4, FFP104, or teneliximab; or an anti-CD40L antibody or antigen-binding protein such as dapirolizumab pegol, dazodalibep [VIB4920], frexalimab [INX-021], letolizumab [BMS-986004], MR-1, ruplizumab [BG9588], tegoprubart [AT-1501], toralizumab [IDEC-131], or APB-A1).

[0925] In some embodiments, the present disclosure provides monospecific anti-CD40L antibodies or antigen-binding fragments thereof that specifically bind CD40L (e.g., human CD40L). In some embodiments, the anti-CD40L antibody or antigen-binding fragment thereof comprises the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within the HCVR/LCVR amino acid sequence pair set forth in SEQ ID NOs: 193/197. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Kabat definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the Chothia definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the AbM definition. In some embodiments, the CDRs within the HCVR and/or LCVR are identified according to the IMGT definition.

[0926] In some embodiments, the anti-CD40L antibody or antigen-binding fragment comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 194, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200.

[0927] In some embodiments, the anti-CD40L antibody comprises: an HCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 193; and/or an LCVR having at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 197. In some embodiments, the anti-CD40L antibody comprises an HCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 193. In some

embodiments, the anti-CD40L antibody comprises an LCVR comprising or consisting of the amino acid sequence of SEQ ID NO: 197.

[0928] In some embodiments, the anti-CD40L antibody comprises: a heavy chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 201; and/or a light chain comprising an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 202. In some embodiments, the anti-CD40L antibody comprises a heavy chain comprising or consisting of the amino acid sequence of SEQ ID NO: 201. In some embodiments, the anti-CD40L antibody comprises a light chain comprising or consisting of the amino acid sequence of SEQ ID NO: 202. In some embodiments, the anti-CD40L antibody is tegoprubart.

[0929] The present disclosure also provides multispecific antigen-binding molecules that specifically bind CD40L. In some embodiments, the antigen-binding molecule is a bispecific antigen-binding molecule, e.g., bispecific antibody. Any of the anti-CD40L antibodies disclosed herein can be in bispecific configuration, including a second arm derived from any other anti-CD40L antibody disclosed herein. In some embodiments, the bispecific antigen-binding molecule comprises a first antigen-binding domain (D1) that binds a first epitope of CD40L (e.g., human CD40L), and a second antigen-binding domain (D2) that binds a second epitope of CD40L (e.g., human CD40L). In some embodiments, D1 and D2 do not compete with one another for binding to CD40L (e.g., human CD40L). In some embodiments, D1 and D2 compete with one another for binding to CD40L (e.g., human CD40L).

[0930] In some embodiments, the bispecific antigen-binding molecule comprises two different heavy chain immunoglobulin variable regions, wherein at least one heavy chain immunoglobulin variable region comprises an HCDR1-HCDR2-HCDR3 amino acid sequences set contained within an HCVR amino acid sequence set forth in SEQ ID NO: 193. In some embodiments, the CDRs within the HCVR are identified according to the Kabat definition. In some embodiments, the CDRs are identified according to the Chothia definition. In some embodiments, the CDRs are identified according to the AbM definition. In some embodiments, the CDRs are identified according to the IMGT definition.

[0931] In some embodiments, at least one heavy chain immunoglobulin variable region comprises an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at

least 99% sequence identity to SEQ ID NO: 193. In some embodiments, at least one heavy chain immunoglobulin variable region comprises or consists of the amino acid sequence of SEQ ID NO: 193.

[0932] In some embodiments, the CD40L inhibitor may comprise a CD40L-binding protein comprising two Tn3 proteins fused to human serum albumin. In some embodiments, the CD40L binding protein comprises an amino acid sequence that has at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 203. In some embodiments, the CD40L binding protein comprises or consists of the amino acid sequence set forth in SEQ ID NO: 203. In some embodiments, the CD40L binding protein is dazodalibep.

[0933] In some embodiments, the CD40 inhibitor may comprise a peptide such as but not limited to KGYY15 (see, e.g., Vaitaitis et al., A CD40-targeted peptide controls and reverses type 1 diabetes in NOD mice Diabetologia. 2014 Nov;57(11):2366-73, herein incorporated by reference in its entirety for all purposes), KGYY6 (Vaitaitis et al., A CD40 targeting peptide prevents severe symptoms in Experimental Autoimmune Encephalomyelitis J Neuroimmunol. 2019 Jul 15; 332: 8–15, herein incorporated by reference in its entirety for all purposes) and CD40–CD40L blocking cyclic heptapetide (CLPTRHMAC (SEQ ID NO: 1109)). In some embodiments, the CD40 inhibitor may comprise an oligonucleotide such as but not limited to NJA-730.

[0934] In some embodiments, the CD40 inhibitor may comprise a small molecule inhibitor (e.g., DRI-C21045, BIO8898). In some embodiments, a small-molecule CD40 inhibitor may comprise any small-molecule as described, for example, in J. Chen, et al. Small-Molecule Inhibitors of the CD40-CD40L Costimulatory Protein-Protein Interaction J. Med. Chem., 60 (21) (2017), pp. 8906-8922; L.F. Silvian, et al. Small molecule inhibition of the TNF family cytokine CD40 ligand through a subunit fracture mechanism ACS Chem. Biol., 6 (6) (2011), pp. 636-647; G.M. Vaitaitis, et al.; E. Margolles-Clark, et al. Suramin inhibits the CD40-CD154 costimulatory interaction: a possible mechanism for immunosuppressive effects Biochem. Pharmacol., 77 (7) (2009), pp. 1236-1245; each of which is herein incorporated by reference in its entirety for all purposes.

[0935] The CD40 inhibitor can be used for inhibiting CD40L-induced activation of CD40, e.g., in or on a cell that expresses CD40 (e.g., a B cell, dendritic cell, monocyte, platelet, or macrophage). The CD40 inhibitor are able to suppress host B cell responses to new antigens. In AAV gene therapies, seronegative/naive subjects are dosed with AAV and develop antibody responses to the AAV capsid antigen. This antibody response prevents future re-dosing of AAV

because the antibodies are neutralizing, and the antibody response is sustained for 10+ years. When AAV is co-administered with a CD40 inhibitor, the B cell response is suppressed and anti-AAV IgG and/or IgM responses are significantly suppressed. When a CD40 inhibitor is given during the period of AAV antigen exposure, the anti-AAV antibody response can be suppressed in animals. This allows re-dosing of any AAV gene therapy product.

[0936] In some embodiments, the CD40 inhibitor can prevent antibody formation against an immunogenic delivery vehicle described herein. As a non-limiting example, the CD40 inhibitor can prevent antibody formation against an AAV or portion thereof. The CD40 inhibitor can also prevent antibody formation against certain LNP components (e.g., anti-PEG IgG), which can improve efficacy of LNP redosing. The CD40 inhibitor can also prevent antibody formation against, e.g., a transgene product described herein.

[0937] In some embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof. In some embodiments, the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, and both antigen-binding domains bind to CD40.

Pharmaceutical Compositions

[0938] In another aspect, the present disclosure provides pharmaceutical compositions comprising CD40 antigen-binding molecules, e.g., CD40xCD40 bispecific antigen-binding molecules (e.g., bispecific antibodies), CD40 inhibitors, and/or immunogens (e.g., immunogenic delivery vehicles) disclosed herein, optionally comprising a pharmaceutically acceptable carrier and/or excipient. The pharmaceutical compositions are formulated with one or more pharmaceutically acceptable vehicle, carriers, and/or excipients. Various pharmaceutically acceptable carriers and excipients are well-known in the art. See, e.g., Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

[0939] One exemplary embodiment of the present disclosure comprises a pharmaceutical composition comprising (i) a plasma cell depleting agent, (ii) a B cell depleting agent and/or an immunoglobulin depleting agent, and (iii) a pharmaceutically acceptable carrier and/or excipient. Another exemplary embodiment of the present disclosure comprises a pharmaceutical composition comprising (i) an immunogen, (ii) a plasma cell depleting agent, (iii) optionally, a B cell depleting agent and/or an immunoglobulin depleting agent, and (iv) a pharmaceutically acceptable carrier and/or excipient

[0940] In some embodiments, the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[0941] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[0942] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

[0943] In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[0944] In some embodiments, the immunogenic delivery vehicle is a viral vector.

[0945] In some embodiments, the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, a retrovirus, or an oncolytic virus.

[0946] In some embodiments, the viral vector is AAV. In some embodiments, the viral vector is derived from AAV.

[0947] In some embodiments, the retrovirus is a lentivirus.

[0948] In some embodiments, the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

[0949] In some embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

[0950] In some embodiments, the anti-CD40 antibody is an antagonistic anti-CD40 antibody.

[0951] In some embodiments, the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

[0952] In some embodiments, the anti-CD40xCD40 bispecific antibody comprises:

(a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

(b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

[0953] In some embodiments, D1 and D2 do not compete with one another for binding to human CD40.

[0954] In some embodiments, the anti-CD40xCD40 bispecific antibody:

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life (t1/2) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

[0955] In some embodiments, the anti-CD40xCD40 bispecific antibody inhibits CD40L-induced activation. In some embodiments, the anti-CD40xCD40 bispecific antibody inhibits CD40L-induced activation and does not significantly agonize CD40 in the absence of CD40L.

[0956] In some embodiments, the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8;

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28; and

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38.

[0957] In some embodiments, the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16.

[0958] In some embodiments, the D1 domain comprises:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO:

12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0959] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0960] In some embodiments, the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

[0961] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0962] In some embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22.

[0963] In some embodiments, the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10.

[0964] In some embodiments, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0965] In some embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32.

[0966] In some embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0967] In some embodiments, the anti-CD40xCD40 bispecific antibody comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3

comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0968] In some embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0969] In certain embodiments, the anti-CD40xCD40 bispecific antibody comprises a D1 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32. In certain embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0970] In certain embodiments, the anti-CD40xCD40 bispecific antibody comprises a D2 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In certain embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0971] In certain embodiments, the anti-CD40xCD40 bispecific antibody comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[0972] In certain embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[0973] In some embodiments, the carrier is suitable for intravenous, intramuscular, oral, intraperitoneal, intratumoral, intrathecal, transdermal, topical, or subcutaneous administration.

[0974] In some embodiments, the pharmaceutical composition comprises an injectable preparation, such as a dosage form for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above, in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule.

[0975] The dose of an antigen-binding molecule, a CD40 inhibitor, and/or an immunogen administered to a patient according to the present disclosure may vary depending upon the age and the size of the patient, symptoms, conditions, route of administration, and the like. The dose is typically calculated according to body weight or body surface area. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering pharmaceutical compositions as disclosed herein may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (e.g., Mordenti *et al.*, 1991, *Pharmaceut.*

Res. 8:1351).

[0976] In some embodiments, e.g., for methods and compositions of the present disclosure involving administration of a plasma cell depleting agent which is a bispecific BCMAxCD3 antibody (e.g., REGN5458) to a subject, the dose of the bispecific BCMAxCD3 antibody (or pharmaceutical compositions thereof) is from about 1 mg/kg to about 30 mg/kg, such as from about 1 mg/kg to about 5 mg/kg, about 5 mg/kg to about 10 mg/kg, about 10 mg/kg to about 15 mg/kg, about 15 mg/kg to about 20 mg/kg, about 20 mg/kg to about 25 mg/kg, or about 25 mg/kg to about 30 mg/kg. In some embodiments, the bispecific BCMAxCD3 antibody (e.g., REGN5458) can be administered to the subject at a dose of about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, or about 30 mg/kg. In one specific embodiment, the bispecific BCMAxCD3 antibody (e.g., REGN5458) (or pharmaceutical composition thereof) dose is about 20 mg/kg.

[0977] In some embodiments, e.g., for methods and compositions of the present disclosure involving administration of an immunogen which is an AAV to a subject, the dose of the AAV (or pharmaceutical compositions thereof) administered to a subject is between about $1x10^5$ plaque forming units (pfu) to about $1x10^{15}$ pfu. In some cases, the AAV can be administered to the subject at a dose from about $1x10^8$ pfu to about $1x10^{15}$ pfu, or from about $1x10^{10}$ pfu to about $1x10^{15}$ pfu, or from about $1x10^8$ pfu to about $1x10^{12}$ pfu.

[0978] In some embodiments, the dose of the AAV (or pharmaceutical compositions thereof) administered to the subject is between about $1x10^5$ vg to about $1x10^{16}$ vg. In certain embodiments, the dose of the AAV administered to the subject is between about $1x10^6$ vg to about $1x10^9$ vg, about $1x10^7$ vg to about $1x10^{10}$ vg, about $1x10^8$ vg to about $1x10^{11}$ vg, about $1x10^9$ vg to about $1x10^{12}$ vg, about $1x10^{10}$ vg to about $1x10^{13}$ vg, about $1x10^{11}$ vg to about $1x10^{14}$ vg, about $1x10^{12}$ vg to about $1x10^{15}$ vg, about $1x10^{13}$ vg to about $1x10^{16}$ vg, or about $1x10^{14}$ vg to about $1x10^{16}$ vg. In certain embodiments, the dose of the AAV administered to the subject is between about $1x10^{10}$ vg to about $1x10^{16}$ vg. In certain embodiments, the dose of the AAV administered to the subject is at least about $1x10^6$ vg, at least about $1x10^7$ vg, at least about $1x10^8$ vg, at least about $1x10^9$ vg, at least about $1x10^{10}$ vg, at least about $1x10^{11}$ vg, at least about $1x10^{12}$ vg, at least about $1x10^{12}$ vg, at least about $1x10^{13}$ vg, at least about $1x10^{14}$ vg, or at least about $1x10^{15}$ vg. In certain embodiments, the vg is total vector genome per

subject.

[0979] In some embodiments, the dose of the AAV (or pharmaceutical compositions thereof) administered to the subject is about $1x10^{12}$, $1x10^{13}$, $1x10^{14}$, $1x10^{15}$, and $1x10^{16}$ vector genomes (vg)/mL. Further examples of doses of AAV include about $1x10^{12}$, about $1x10^{13}$, about $1x10^{14}$, about $1x10^{15}$, and about $1x10^{16}$ vector genomes (vg)/mL, or between about $1x10^{12}$ to about $1x10^{16}$, between about $1x10^{12}$ to about $1x10^{15}$, between about $1x10^{12}$ to about $1x10^{14}$, between about $1x10^{12}$ to about $1x10^{13}$, between about $1x10^{13}$ to about $1x10^{16}$, between about $1x10^{14}$ to about $1x10^{16}$, between about $1x10^{15}$ to about $1x10^{16}$, or between about $1x10^{13}$ to about $1x10^{15}$ vg/mL.

[0980] Other examples of doses of AAV (or pharmaceutical compositions thereof) include about $1x10^{12}$, about $1x10^{13}$, about $1x10^{14}$, about $1x10^{15}$, and about $1x10^{16}$ vector genomes (vg)/kg of body weight, or between about $1x10^{12}$ to about $1x10^{16}$, between about $1x10^{12}$ to about $1x10^{15}$, between about $1x10^{12}$ to about $1x10^{14}$, between about $1x10^{12}$ to about $1x10^{13}$, between about $1x10^{13}$ to about $1x10^{16}$, between about $1x10^{14}$ to about $1x10^{16}$, between about $1x10^{15}$ to about $1x10^{16}$, or between about $1x10^{13}$ to about $1x10^{15}$ vg/kg of body weight.

[0981] In one example, the AAV dose (or pharmaceutical compositions thereof) is between about $1x10^{13}$ to about $1x10^{14}$ vg/mL or vg/kg. In another example, the AAV dose is between about $1x10^{12}$ to about $1x10^{13}$ vg/mL or vg/kg (e.g., between about $1x10^{12}$ to about $1x10^{13}$ vg/kg). In another example, the AAV dose is between about $1x10^{12}$ to about $1x10^{14}$ vg/mL or vg/kg (e.g., between about $1x10^{12}$ to about $1x10^{14}$ vg/kg).

[0982] In one specific embodiment, the AAV dose (or pharmaceutical composition thereof) is about $3x10^{11}$ vg/kg. In one specific embodiment, the AAV dose (or pharmaceutical composition thereof) is about $6x10^{11}$ vg/kg. In another specific embodiment, the AAV dose (or pharmaceutical composition thereof) is about $9x10^{11}$ vg/kg. In another specific embodiment, the AAV dose (or pharmaceutical composition thereof) is about $3x10^{12}$ vg/kg. In one specific embodiment, the AAV dose (or pharmaceutical composition thereof) is about $1x10^{13}$ vg/kg. In another specific embodiment, the AAV dose (or pharmaceutical composition thereof) is about $6x10^{13}$ vg/kg.

[0983] Various delivery systems are known and can be used to administer the pharmaceutical composition, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing, e.g., recombinant viruses comprising any components of the compositions disclosed herein, and a soluble carrier system that takes advantage of receptor mediated endocytosis (see, e.g., Wu et al., 1987, *J. Biol. Chem.* 262:4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal,

intratumoral, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. In some embodiments, a pharmaceutical composition as disclosed herein is administered intravenously. In some embodiments, a pharmaceutical composition as disclosed herein is administered subcutaneously. In some embodiments, a pharmaceutical composition as disclosed herein is administered intratumorally.

[0984] In some embodiments, an antigen-binding molecule, a CD40 inhibitor, and/or an immunogen, or a pharmaceutical thereof, is contained within a container. Thus, in another aspect, containers comprising an antigen-binding molecule and/or pharmaceutical composition as disclosed herein are provided. For example, in some embodiments, an antibody and/or pharmaceutical composition is contained within a container selected from the group consisting of a glass vial, a syringe, a pen delivery device, and an autoinjector.

[0985] In some embodiments, an antigen-binding molecule, a CD40 inhibitor, and/or an immunogen, or pharmaceutical composition of the present disclosure is delivered, e.g., subcutaneously or intravenously, such as with a standard needle and syringe. In some embodiments, the syringe is a pre-filled syringe. In some embodiments, a pen delivery device or autoinjector is used to deliver a pharmaceutical composition of the present disclosure (e.g., for subcutaneous delivery). A pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0986] Examples of suitable pen and autoinjector delivery devices include, but are not limited to, AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™,

OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany). Examples of disposable pen delivery devices having applications, e.g., in subcutaneous delivery of a pharmaceutical composition of the present invention include, but are not limited to, the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL).

[0987] In some embodiments, the pharmaceutical composition is delivered using a controlled release system. In one embodiment, a pump may be used (see e.g., Langer, supra; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0988] In some embodiments, pharmaceutical compositions for use as described herein are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. In some embodiments, the amount of the antigen-binding molecule contained in the dosage form is about 5 to about 1000 mg, e.g., from about 5 to about 500 mg, from about 5 to about 100 mg, or from about 10 to about 250 mg.

[0989] CD40 antigen-binding molecules, CD40 inhibitors and/or immunogens (e.g., immunogenic delivery vehicles) introduced into the subject or cell can be provided in compositions comprising a carrier, thereby increasing the stability of the introduced molecules, e.g., prolonging the period under given conditions of storage (e.g., -20°C, 4°C, or ambient temperature) for which degradation products remain below a threshold, such below 0.5% by weight of the starting nucleic acid or protein; or increasing the stability *in vivo*. Non-limiting examples of such carriers include poly(lactic acid) (PLA) microspheres, poly(D,L-lactic-coglycolic-acid) (PLGA) microspheres, liposomes, micelles, inverse micelles, lipid cochleates, and lipid microtubules.

[0990] Various methods and compositions are provided herein to allow for introduction of a molecule (e.g., a nucleic acid or protein) into a cell or subject. Methods for introducing molecules into various cell types are known and include, for example, stable transfection

methods, transient transfection methods, and virus-mediated methods.

[0991] Transfection protocols, as well as protocols for introducing molecules into cells, may vary. Non-limiting transfection methods include chemical-based transfection methods using liposomes; nanoparticles; calcium phosphate (Graham et al. (1973) *Virology* 52 (2): 456–67, Bacchetti et al. (1977) *Proc. Natl. Acad. Sci. U.S.A.* 74 (4):1590–4, and Kriegler, M (1991). Transfer and Expression: A Laboratory Manual. New York: W. H. Freeman and Company. pp. 96–97); dendrimers; or cationic polymers such as DEAE-dextran or polyethylenimine. Non-chemical methods include electroporation, sonoporation, and optical transfection. Particle-based transfection can include the use of a gene gun or magnet-assisted transfection (Bertram (2006) *Current Pharmaceutical Biotechnology* 7, 277–28). Viral methods can also be used for transfection.

[0992] Introduction of nucleic acids or proteins into a cell can also be mediated by electroporation, by intracytoplasmic injection, by viral infection, by adenovirus, by adeno-associated virus, by lentivirus, by retrovirus, by transfection, by lipid-mediated transfection, or by nucleofection. Nucleofection is an improved electroporation technology that enables nucleic acid substrates to be delivered not only to the cytoplasm, but also through the nuclear membrane and into the nucleus. In addition, use of nucleofection in the methods disclosed herein typically requires much fewer cells than regular electroporation (e.g., only about 2 million cells as compared with 7 million cells by regular electroporation). In one example, nucleofection is performed using the LONZA® NUCLEOFECTOR™ system.

[0993] Introduction of molecules (e.g., nucleic acids or proteins) into a cell (e.g., a zygote) can also be accomplished by microinjection. In zygotes (i.e., one-cell stage embryos), microinjection can be into the maternal and/or paternal pronucleus or into the cytoplasm. If the microinjection is into only one pronucleus, the paternal pronucleus is preferable due to its larger size.

[0994] Other methods for introducing molecules (e.g., nucleic acid or proteins) into a cell or subject can include, for example, vector delivery, particle-mediated delivery, exosome-mediated delivery, lipid-nanoparticle-mediated delivery, cell-penetrating-peptide-mediated delivery, or implantable-device-mediated delivery. As specific examples, a nucleic acid or protein can be introduced into a cell or subject in a carrier such as a poly(lactic acid) (PLA) microsphere, a poly(D,L-lactic-coglycolic-acid) (PLGA) microsphere, a liposome, a micelle, an inverse micelle, a lipid cochleate, or a lipid microtubule. Some specific examples of delivery to a subject include hydrodynamic delivery, virus-mediated delivery (e.g., adeno-associated virus (AAV)-mediated delivery), and lipid-nanoparticle-mediated delivery.

[0995] Introduction of nucleic acids or proteins into cells or subjects can be accomplished by

hydrodynamic delivery (HDD). For gene delivery to parenchymal cells, only essential DNA sequences need to be injected via a selected blood vessel, eliminating safety concerns associated with current viral and synthetic vectors. When injected into the bloodstream, DNA is capable of reaching cells in the different tissues accessible to the blood. Hydrodynamic delivery employs the force generated by the rapid injection of a large volume of solution into the incompressible blood in the circulation to overcome the physical barriers of endothelium and cell membranes that prevent large and membrane-impermeable compounds from entering parenchymal cells. In addition to the delivery of DNA, this method is useful for the efficient intracellular delivery of RNA, proteins, and other small compounds *in vivo*. *See, e.g.*, Bonamassa et al. (2011) *Pharm. Res.* 28(4):694-701, herein incorporated by reference in its entirety for all purposes.

[0996] Introduction of nucleic acids can also be accomplished by virus-mediated delivery, such as AAV-mediated delivery or lentivirus-mediated delivery. Other exemplary viruses/viral vectors which can be useful in accomplishing virus-mediated delivery include retroviruses, adenoviruses, vaccinia viruses, poxviruses, and herpes simplex viruses. The viruses can infect dividing cells, non-dividing cells, or both dividing and non-dividing cells. The viruses can integrate into the host genome or, alternatively, do not integrate into the host genome. Such viruses can also be engineered to have reduced immunity. The viruses can be replication-competent or can be replication-defective (e.g., defective in one or more genes necessary for additional rounds of virion replication and/or packaging). Viruses can cause transient expression or longer-lasting expression. Viral vectors may be genetically modified from their wild type counterparts. For example, the viral vector may comprise an insertion, deletion, or substitution of one or more nucleotides to facilitate cloning or such that one or more properties of the vector is changed. Such properties may include packaging capacity, transduction efficiency, immunogenicity, genome integration, replication, transcription, and translation. In some examples, a portion of the viral genome may be deleted such that the virus is capable of packaging exogenous sequences having a larger size. In some examples, the viral vector may have an enhanced transduction efficiency. In some examples, the immune response induced by the virus in a host may be reduced. In some examples, viral genes (such as integrase) that promote integration of the viral sequence into a host genome may be mutated such that the virus becomes non-integrating. In some examples, the viral vector may be replication defective. In some examples, the viral vector may comprise exogenous transcriptional or translational control sequences to drive expression of coding sequences on the vector. In some examples, the virus may be helper-dependent. For example, the virus may need one or more helper virus

to supply viral components (such as viral proteins) required to amplify and package the vectors into viral particles. In such a case, one or more helper components, including one or more vectors encoding the viral components, may be introduced into a host cell or population of host cells along with the vector system described herein. In other examples, the virus may be helper-free. For example, the virus may be capable of amplifying and packaging the vectors without a helper virus. In some examples, the vector system described herein may also encode the viral components required for virus amplification and packaging.

[0997] Exemplary viral titers (e.g., AAV titers) include about 10^{12}, about 10^{13}, about 10^{14}, about 10^{15}, and about 10^{16} vector genomes (vg)/mL, or between about 10^{12} to about 10^{16}, between about 10^{12} to about 10^{15}, between about 10^{12} to about 10^{14}, between about 10^{12} to about 10^{13}, between about 10^{13} to about 10^{16}, between about 10^{14} to about 10^{16}, between about 10^{15} to about 10^{16}, or between about 10^{13} to about 10^{15} vg/mL. Other exemplary viral titers (e.g., AAV titers) include about 10^{12}, about 10^{13}, about 10^{14}, about 10^{15}, and about 10^{16} vector genomes (vg)/kg of body weight, or between about 10^{12} to about 10^{16}, between about 10^{12} to about 10^{15}, between about 10^{12} to about 10^{14}, between about 10^{12} to about 10^{13}, between about 10^{13} to about 10^{16}, between about 10^{14} to about 10^{16}, between about 10^{15} to about 10^{16}, or between about 10^{13} to about 10^{15} vg/kg of body weight. In one example, the viral titer is between about 10^{13} to about 10^{14} vg/mL or vg/kg. In another example, the viral titer is between about 10^{12} to about 10^{13} vg/mL or vg/kg (e.g., between about 10^{12} to about 10^{13} vg/kg). In another example, the viral titer is between about 10^{12} to about 10^{14} vg/mL or vg/kg (e.g., between about 10^{12} to about 10^{14} vg/kg). For example, the viral titer can be between about 1.5E12 to about 1.5E13 vg/kg, can be about 1.5E12 vg/kg, or can be about 1.5E13 vg/kg. In another example, the viral titer is about 1E12 to about 2E14 vg/kg. In another example, the viral titer is about 3E11 vg/kg to about 5E13 vg/kg. In some embodiments, the viral titer is about 1E13 vg/kg. AAVs for use in the methods are discussed in more detail elsewhere herein.

[0998] In yet another aspect, the present disclosure includes compositions and therapeutic formulations comprising any of the exemplary antigen binding molecules, e.g., antibodies and bispecific antigen-binding molecules, CD40 inhibitors, and/or immunogens (e.g., immunogenic delivery vehicles such as, e.g., AAV) described herein in combination with one or more additional therapeutic agents, and methods of treatment comprising administering such combinations to subjects in need thereof. In some embodiments, the additional therapeutic agent(s) is an immunomodulatory agent. An immunomodulatory agent as disclosed herein can include, without limitation, a plasma cell depleting agent, a B cell depleting agent, or an immunoglobulin depleting agent, or any combination thereof. In some embodiments, the

additional therapeutic agent(s) is an anti-inflammatory agent. In some embodiments, the additional therapeutic agent(s) is a therapeutic procedure. Such therapeutic procedures can comprise, without limitation, a plasma-based therapeutic procedure such as, but not limited to plasmapheresis, therapeutic plasma exchange, or immunoadsorption, or any combination thereof. In some embodiments, the additional therapeutic agent(s) is immunosuppressive therapy. In some embodiments, the additional therapeutic agent(s) is a surgical procedure.

[0999] Exemplary additional therapeutic agents that may be combined with or administered in combination with an antigen-binding molecule of the present disclosure include, e.g., another CD40-CD40L inhibitor (e.g., an anti-CD40 antibody such as iscalimab [CFZ-533], ravagalimab [ABBV-323]/Ab102, BI-655064, bleselumab [ASKP1240], ch5D12, lucatumumab [HCD122 or CHIR12.12], CHIR-5.9, abiprubart [KPL-404] PG102/FFP104, BIIB063, BMS3h-37, BMS3h-38, BMS3h-56, BMS3h-198 V19, V15, h2C10 and variants thereof, Ab101, Antibody A, Antibody B, Antibody C, G28.5, Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3], Y12XX-hz42 [Vh-hzl4;Vk-hz3] or teneliximab; or an anti-CD40L antibody or antigen-binding protein such as dapirolizumab pegol, dazodalibep [VIB4920], frexalimab [INX-021], letolizumab [BMS-986004], MR-1, ruplizumab [BG9588], tegoprubart [AT-1501], or toralizumab [IDEC-131] or APB-A1; or a CD40 inhibitor peptide [such as but not limited to KGYY15, KGYY6, or CD40–CD40L blocking cyclic heptapetide (CLPTRHMAC (SEQ ID NO: 1109))]; or a CD40 inhibitor oligonucleotide [e.g., NJA-730]; or a small molecule inhibitor [e.g., DRI-C21045, BIO8898 or any small-molecule as described, for example, in J. Chen, et al. Small-Molecule Inhibitors of the CD40-CD40L Costimulatory Protein-Protein Interaction J. Med. Chem., 60 (21) (2017), pp. 8906-8922; L.F. Silvian, et al. Small molecule inhibition of the TNF family cytokine CD40 ligand through a subunit fracture mechanism ACS Chem. Biol., 6 (6) (2011), pp. 636-647; G.M. Vaitaitis, et al.; E. Margolles-Clark, et al. Suramin inhibits the CD40-CD154 costimulatory interaction: a possible mechanism for immunosuppressive effects Biochem. Pharmacol., 77 (7) (2009), pp. 1236-1245; each of which is herein incorporated by reference in its entirety for all purposes]).

[01000] Non-limiting examples of plasma cell depleting agent(s), B cell depleting agent(s), immunoglobulin depleting agent(s), and suitable combinations thereof, as well as combinations involving plasmapheresis, therapeutic plasma exchange, and/or immunoadsorption are described in more detail elsewhere herein.

[01001] In one example, a viral titer is about 1E12 to about 2E14 vg/kg (e.g., without plasma cell depletion and redosing). In another example, the viral titer is about 3E11 vg/kg to about 5E13 vg/kg (e.g., 2-3X lower with plasma cell depletion, due to 2-3 separate administrations with redosing). Use of the plasma cell depleting agents or combinations comprising plasma cell

depleting agents in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) allows redosing, permitting step-wise dosing with lower doses (e.g., step-wise dosing of 2-3 doses with each dose being 2-3X lower than a dose would be in a one-time administration (e.g., without plasma cell depletion). In another example, the viral titer is about 1E12 to about 2E14 vg/kg (e.g., without CD40 inhibition and plasma cell depletion and redosing). In another example, the viral titer is about 3E11 vg/kg to about 5E13 vg/kg (e.g., 2-3X lower with CD40 inhibition and plasma cell depletion, due to 2-3 separate administrations with redosing). Use of CD40 inhibition and the plasma cell depleting agents or combinations comprising plasma cell depleting agents in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) allows redosing, permitting step-wise dosing with lower doses (e.g., step-wise dosing of 2-3 doses with each dose being 2-3X lower than a dose would be in a one-time administration (e.g., without CD40 inhibition and plasma cell depletion).

[01002] The additional therapeutically active component(s) may be administered just prior to, concurrent with, or shortly after the administration of an antigen-binding molecule, a CD40 inhibitor, and/or an immunogen of the present disclosure. For the purposes of the present disclosure, such administration regimens are considered the administration of an antigen-binding molecule "in combination with" an additional therapeutically active component.

[01003] The present disclosure includes pharmaceutical compositions in which an antigen-binding molecule, a CD40 inhibitor, and/or an immunogen (e.g., an immunogenic delivery vehicle) of the present invention is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

[01004] Therapeutic or pharmaceutical compositions comprising the compositions disclosed herein can be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. *See also* Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) *J. Pharm. Sci. Technol.* 52:238-311. In certain embodiments, the pharmaceutical compositions are non-pyrogenic.

Kits

[01005] The present disclosure further comprises a kit which may comprise any of various

compositions of the present disclosure, including the antigen-binding molecules, CD40 inhibitors, immunogens (e.g., immunogenic delivery vehicles), or pharmaceutical compositions thereof, of the disclosure. Such kits may further comprise plasma cell depleting agents (optionally in combination with B cell depleting agents and/or immunoglobulin depleting agents) or pharmaceutical compositions thereof, of the disclosure.

[01006] One exemplary embodiment of the present disclosure comprises a kit comprising (i) a plasma cell depleting agent, (ii) a B cell depleting agent and/or an immunoglobulin depleting agent, and (iii) optionally, instructions for use. Another exemplary embodiment of the present disclosure comprises a kit comprising (i) an immunogen, (ii) a plasma cell depleting agent, (iii) optionally a B cell depleting agent and/or an immunoglobulin depleting agent, and (iv) optionally, instructions for use.

[01007] In one aspect, the present disclosure may include a kit comprising, for example: (a) a container that contains a pharmaceutical composition disclosed herein, for example, a pharmaceutical composition in solution or in lyophilized form; (b) optionally, a second container containing a diluent or reconstituting solution for the lyophilized formulation; and/or (c) optionally, instructions for (i) use of the solution or (ii) reconstitution and/or use of the lyophilized formulation.

[01008] In some embodiments, the kit may further comprise, for example, without limitation, one or more of (i) a buffer, (ii) a diluent, (iii) a filter, (iv) a needle, and/or (v) a syringe. As a non-limiting example, the container may be a bottle, a vial, a syringe or test tube. In some embodiments, the container may be a multi-use container. In some the pharmaceutical composition may be lyophilized.

[01009] Kits of the present disclosure may comprise a lyophilized formulation of the present disclosure in a suitable container and instructions for its reconstitution and/or use. Suitable containers include, for example, bottles, vials (e.g. dual chamber vials), syringes (such as dual chamber syringes) and test tubes. The container may be formed from a variety of materials such as glass or plastic. The kit and/or container may contain instructions on or associated with the container that indicate directions for reconstitution of the lyophilized formulation and/or use of the kit. For example, the label may indicate that the lyophilized formulation is to be reconstituted to an appropriate peptide concentration. The label may indicate that the formulation is useful or intended for any route of administration disclosed herein, e.g., parenteral administration routes disclosed herein.

[01010] The container holding the formulation may be a multi-use vial, which may allow for repeat administrations (e.g., from 2-6 administrations) of the reconstituted formulation. The kit

may further comprise a second container comprising a suitable diluent (e.g., sodium bicarbonate solution).

[01011] Upon mixing of the diluent and the lyophilized formulation, the final peptide concentration in the reconstituted formulation is reached. The kit may further include other materials desirable from a commercial and/or user standpoint, including, for example, without limitation, other buffers, diluents, filters, needles, syringes, and/or package inserts which may comprise, e.g., instructions for use.

[01012] Kits of the present disclosure may have a single container that contains the formulation of the pharmaceutical compositions according to the present disclosure with or without other components (e.g., other compounds or pharmaceutical compositions of these other compounds) or may have a distinct container for each component.

[01013] In some embodiments, kits of the disclosure may include a formulation of the disclosure packaged for use in combination with the coadministration of a second compound (such as adjuvants (e.g., GM-CSF, a chemotherapeutic agent, a natural product, a hormone or antagonist, an anti-angiogenesis agent or inhibitor, an apoptosis-inducing agent or a chelator) or a pharmaceutical composition thereof. The components of the kit may be pre-complexed or each component may be in a separate distinct container prior to administration to a patient. The components of the kit may be provided in one or more liquid solutions. A liquid solutions described herein may be an aqueous solution, for example, a sterile aqueous solution. The components of the kit may also be provided as solids, which may be converted into liquids such as by addition of suitable solvents, which may be provided in another distinct container.

[01014] The container of a therapeutic kit may be a vial, test tube, flask, bottle, syringe, or any other means of enclosing a solid or liquid. When there is more than one component, the kit may contain a second vial or other container, which may allow for separate dosing. The kit may also contain another container for a pharmaceutically acceptable liquid. In some embodiment, a kit may contain an apparatus (e.g., one or more needles, syringes, eye droppers, pipettes, etc.), which may allow for administration of the agents of the disclosure that are components of the present kit.

Therapeutic Uses

[01015] In another aspect, the present disclosure provides for methods of using the antigen-binding molecules of the disclosure (e.g., CD40xCD40 bispecific antigen-binding molecules disclosed herein). In some embodiments, the present disclosure provides methods of inhibiting CD40L-induced activation of CD40, e.g., in or on a cell that expresses CD40 (e.g., a B cell,

dendritic cell, monocyte, platelet, or macrophage). In some embodiments, the method comprises contacting a CD40-expressing cell with a CD40xCD40 bispecific antigen-binding molecule as disclosed herein.

[01016] In another aspect, the present disclosure provides for methods of using a CD40 inhibitor of the disclosure. In some embodiments, the present disclosure provides methods for inhibiting an immune response to an immunogen in a subject in need thereof, the methods comprising administering to the subject an effective amount of a CD40 inhibitor. In some embodiments, the present disclosure provides methods for inhibiting generation of neutralizing antibodies to an immunogen in a subject in need thereof, the methods comprising administering to the subject an effective amount of a CD40 inhibitor. In some embodiments of methods of the disclosure comprising administering to the subject an effective amount of a CD40 inhibitor and an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), the subject has a pre-existing immunity against the immunogen (e.g., AAV). In some embodiments, the present disclosure provides methods for increasing effectiveness of re-administration of an immunogen to a subject in need thereof, the methods comprising administering to the subject an effective amount of a CD40 inhibitor. The term "re-administering" is used synonymously and interchangeably with the term "re-dosing" herein. In some embodiments, the present disclosure provides methods for increasing or maintaining the level of a transgene expression in a subject in need thereof, and the transgene is delivered to the subject via an immunogenic delivery vehicle, the methods comprising administering to the subject an effective amount of a CD40 inhibitor.

[01017] In some embodiments, a CD40 inhibitor, which can be useful in any of the methods or compositions disclosed herein may be further used in combination with a plasmapheresis, therapeutic plasma exchange, and/or immunoadsorption.

[01018] In some embodiments, the present disclosure provides methods of treating, ameliorating, or preventing a CD40-mediated disease or condition by administering a therapeutically effective amount of a CD40 antigen-binding molecule, e.g., a CD40xCD40 bispecific antigen-binding molecule, to a subject in need thereof. A CD40-mediated disease or condition, as used herein, is any disease or condition that is caused or exacerbated by an activity of CD40 (e.g., activation of downstream signaling due to CD40 binding to its ligand CD40L). In some embodiments, a CD40-mediated disease or condition is due to a mutation in CD40 or CD40L, or in a gene in the CD40 signaling pathway.

[01019] In some embodiments, a CD40-mediated disease or condition is an autoimmune disease or condition, an inflammatory disease or condition, a cardiovascular disease or

condition, or organ transplant. In some embodiments, the CD40-mediated disease or condition is an autoimmune disease or condition. In some embodiments, the CD40-mediated disease or condition is Addison's disease, autoimmune hemolytic anemia, autoimmune thyroid disease (e.g., thyroiditis, Graves' disease, or Hashimoto's thyroiditis), Crohn's disease, diabetes (e.g., type 1 diabetes), experimental autoimmune encephalomyelitis (EAE), Focal segmental glomerulosclerosis (FSGS), glomerulonephritis, Guillain-Barre syndrome, graft versus host disease (GVHD) (e.g., acute GVHD or chronic GVHD), hemolytic anemia, hidradenitis suppurativa (HS), immune thrombocytopenia, inflammatory bowel disease, inflammatory neuropathy (e.g., acute inflammatory demyelinating polyneuropathy (AIDP) or chronic inflammatory demyelinating polyneuropathy (CIDP)), Kawasaki disease, lupus nephritis, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, neuromyelitis optica spectrum disorder, organ transplantation (e.g., kidney or liver transplant), pemphigus, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Sjogren's syndrome, skin graft, spondyloarthropathies, systemic lupus erythematosus, systemic sclerosis, transplant rejection, vasculitis, ANCA-associated vasculitis (e.g., granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and/or eosinophilic GPA (EGPA)), ulcerative colitis, or Wegener granulomatosis.

[01020] In some embodiments, administration of a CD40 antigen-binding molecule, e.g., a CD40xCD40 bispecific antigen-binding molecule (e.g., as disclosed in any one of **Tables 3-6**) prevents or delays the increase of disease symptoms or the progression of disease in a subject having a CD40-mediated disease or condition.

Exemplary Uses of CD40 inhibitors

[01021] In one aspect, the present disclosure provides for methods for inhibiting an immune response to an immunogen in a subject in need thereof, the method comprising administering to the subject an effective amount of a CD40 inhibitor, e.g., an antigen-binding molecule of the present disclosure such as a monospecific, bispecific, or multispecific antibody, that specifically binds to CD40, or an antigen-binding fragment thereof. In some embodiments, a CD40 inhibitor can comprise an CD40 antigen-binding molecule as disclosed herein (e.g., a CD40xCD40 bispecific antigen-binding molecule, e.g., as disclosed in any one of **Tables 3-6**). The term "immune response" refers to a response of a cell of the immune system (e.g., a B-cell, T-cell, macrophage or polymorphonucleocyte) to a stimulus such as an immunogen, e.g., an antigen (e.g., a viral antigen). Active immune responses can involve differentiation and proliferation of immunocompetent cells, which leads to synthesis of antibodies or the development of cell-

mediated reactivity, or both. An active immune response can be mounted by the host after exposure to an antigen (e.g., by infection or by vaccination). An active immune response can be contrasted with passive immunity, which can be acquired through the transfer of substances such as, e.g., an antibody, a transfer factor, a thymic graft, and/or a cytokine from an actively immunized host to a non-immune host.

[01022] In some embodiments, the immune response is a humoral (antibody producing) immune response and/or a cell-mediated immune response in a subject (e.g., a human).

[01023] In some embodiments, a CD40 inhibitor may inhibit an immune response by a cell (e.g., an immune cell such as by a B cell or a T cell) or by an immune system of a subject (e.g., a human) which can be elicited by an immunogen.

[01024] As used herein, the term "immunogen" refers to any molecule that is capable of eliciting an immune response. Non-limiting examples of immunogens include immunogenic delivery vehicles such as viral vectors also termed herein "viral particles" (e.g., viral vectors derived from adeno-associated viruses (AAV), adenoviruses, retroviruses [e.g., lentiviruses], or oncolytic viruses [e.g., an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus]) or portions thereof (e.g., capsid proteins), virus-like particles (VLPs), non-viral vectors (e.g., bacteriophages [such as lambda (X) bacteriophage, EMBL bacteriophage; bacterial vectors such as pBs, phagescript, PsiX174, pBluescript SK, pBs KS, pNH8a, pNH16a, pNH18a, pNH46a; pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5]; eukaryotic vectors [such as pWLneo, pSV2cat, pOG44, PXR1, pSG, pSVK3, pBPV, pMSG and pSVL]; transposons [such as Sleeping Beauty transposon and PiggyBac transposon]; bacterial vectors, fungal vectors, and protozoal vectors), liposomes, lipid nanoparticles (LNPs), non-lipid nanoparticles, and other carriers. Non-limiting examples of immunogens also include polypeptide molecules (e.g., proteins [e.g., therapeutic proteins or antibodies or fragments thereof], peptides), polynucleotide molecules (e.g., mRNAs, interfering nucleic acid molecules [RNAi, siRNA, shRNA], miRNAs, antisense oligonucleotides, ribozymes, aptamers, mixmers, or multimers), antigen-binding molecules fused to a payload, as well as naturally occurring or modified bacteria, fungi, protozoa, parasites, helminths, ectoparasites, or other microorganisms (including bacteria, fungi and other microorganisms found in microbiota). Glycans and lipids are further encompassed by the term immunogen as used herein.

[01025] In some embodiments, the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

[01026] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

[01027] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or transgene product(s). In some embodiments, the immunogenic delivery vehicle is a viral vector. In some embodiments, the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

[01028] In some embodiments, a CD40 inhibitor may inhibit an immune response by a cell (e.g., an immune cell such as by a B cell or a T cell) or by an immune system of a subject (e.g., a human) which can be elicited by an immunogenic delivery vehicle.

[01029] In some embodiments, an immunogenic delivery vehicle, e.g., a viral particle or vector disclosed herein, may comprise, e.g., one or more of a heterologous and/or recombinant nucleotide sequence(s) of interest (e.g., a nucleotide sequence encoding a gene, or portion thereof, desired to be expressed in a cell targeted by the viral particle (e.g., a transgene), which nucleotide sequence of interest may be, e.g., DNA or RNA). In some embodiments, the nucleotide sequence can encode a polypeptide of interest disclosed herein. In various embodiments, the nucleotide sequence can encode a transgene product comprising one or more therapeutic agents (e.g., therapeutic proteins or polypeptides) described herein. In some embodiments, a CD40 inhibitor may inhibit an immune response which can be elicited by a polypeptide of interest, e.g., a transgene product, disclosed herein.

[01030] In one aspect, the present disclosure provides a method for increasing or maintaining the level of AAV transduction in a target cell and/or tissue, e.g., a target cell and/or tissue within or derived from a subject in need thereof, the method comprising contacting the target cell and/or tissue with, and/or administering to the subject, an effective amount of a CD40 inhibitor. In some embodiments, the level of AAV transduction in the target cell and/or tissue is increased or maintained by inhibiting an immune response to the AAV in the subject. In some embodiments, the level of AAV transduction is increased or maintained in the target cell and/or tissue by inhibiting antibody responses to the AAV in the subject.

[01031] In some embodiments, the level of AAV transduction in the target cell and/or tissue is increased or maintained by inhibiting an immune response to the AAV in a subject. As a non-limiting example, the level of AAV transduction in the target cell and/or tissue may be increased by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about

25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The level of AAV transduction may be increased in the target cell and/or tissue by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The level AAV transduction may be increased in the target cell and/or tissue by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%. In some embodiments, the level of AAV transduction in the target cell and/or tissue is maintained by inhibiting an immune response to the AAV in the subject.

[01032] In some embodiments, the level of AAV transduction in the target cell and/or tissue is increased or maintained by inhibiting antibody responses to the AAV in a subject. As a non-limiting example, the level of AAV transduction in the target cell and/or tissue may be increased by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The level of AAV transduction may be increased in the target cell and/or tissue by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The level AAV transduction may be increased in the target cell and/or tissue by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%. In some embodiments, the level of AAV transduction in the target cell and/or tissue is maintained by inhibiting antibody responses to the AAV in the subject.

[01033] In one aspect, the present disclosure provides a method for increasing or maintaining the level of a transgene expression in a subject in need thereof, the method comprising administering to the subject an effective amount of a CD40 inhibitor.

[01034] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

[01035] In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[01036] In some embodiments, the transgene is delivered to the subject via an immunogenic delivery vehicle (e.g., AAV).

[01037] In some embodiments, the level of transgene expression is increased or maintained by inhibiting an immune response to the immunogenic delivery vehicle and/or by inhibiting an immune response to the transgene product(s) (e.g., a polypeptide or polynucleotide encoded by the transgene). As a non-limiting example, the level of transgene expression may be increased by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The level of transgene expression may be increased by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The level of transgene expression may be increased by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01038] In some embodiments, the level of transgene expression is increased or maintained by inhibiting antibody responses to the transgene product(s) (e.g., a polypeptide or polynucleotide encoded by the transgene). In some embodiments, anti-transgene antibody responses may be inhibited by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. Anti-transgene antibody responses may be inhibited by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about

90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. Anti-transgene antibody responses may be inhibited by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01039] In some embodiments, an immune response may be inhibited in a subject following immunogen (e.g., AAV) dosing and/or re-dosing. The immune response may be inhibited by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The immune response may be inhibited by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The immune response may be inhibited by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or even 100%. In some embodiments, an immune response may be inhibited in a subject following immunogen (e.g., AAV) dosing and/or re-dosing in the subject to achieve levels equivalent to, or even below, those of an AAV-naïve subject.

[01040] In some embodiments, the immune response to the immunogenic delivery vehicle and/or the immune response to the polypeptide or polynucleotide encoded by the transgene may be inhibited by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The immune response to the immunogenic delivery vehicle and/or the immune response to the polypeptide or polynucleotide encoded by the transgene may be inhibited by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than

95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The immune response to the immunogenic delivery vehicle and/or the immune response to the polypeptide or polynucleotide encoded by the transgene may be inhibited by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01041] In some embodiments, the CD40 inhibitor described herein can block or suppress CD40 and/or CD40-mediated cellular signaling pathways and/or mechanisms, e.g., cellular signaling pathways and/or mechanisms associated with an immune response. When the antigen-binding molecule blocks CD40 and/or CD40-mediated signaling and/or mechanisms, such blockade can inhibit an immune response (e.g., a humoral and/or cell-mediated immune response) in a subject. The inhibition of an immune response may comprise, for example, disruption of B cell germinal centers and/or prevention of generation of immunogen-specific germinal center B cells. In such instances, without limitation, the number and/or frequency of immunogen-specific germinal center B cells and/or the total number and/or frequency of germinal center B cells may be reduced as compared to when the antigen-binding molecule is absent. In some embodiments, the CD40 inhibitor described herein can reduce alanine aminotransferase activity (ALT) in serum. In some embodiments, the CD40 inhibitor described herein can reduce liver injury associated with anti-transgene T cell responses.

[01042] In some embodiments of the methods for inhibiting an immune response to an immunogen described herein, the inhibiting of the immune response can comprise suppression of numbers and/or frequencies of an immunogen-specific B cell, e.g., an immunogen-specific germinal center B cell. In some embodiments of the methods for inhibiting an immune response to an immunogen described herein, the inhibiting of the immune response can comprise suppression of the magnitude and duration of an anti-AAV8 antibody response.

[01043] In some embodiments, the number and/or frequency of immunogen-specific germinal center B cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The number and/or frequency of immunogen-specific germinal center B cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more

than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The number and/or frequency of immunogen-specific germinal center B cells may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01044] In some embodiments, the total number and/or frequency of germinal center B cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The total number and/or frequency of germinal center B cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The total number and/or frequency of germinal center B cells may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01045] In some embodiments, immunogen-specific germinal center B cells and/or germinal center B cells are eliminated. In some embodiments, the number and/or frequency of memory B cells, naïve B cells and/or plasma cells are not impacted by the CD40 inhibitor, e.g., the number and/or frequency of memory B cells, naïve B cells and/or plasma cells is the same in the presence of the CD40 inhibitor as compared to when the CD40 inhibitor is absent.

[01046] In some embodiments, the inhibition of an immune response may comprise suppression of a T cell response to an immunogen. In such instances, without limitation, the number and/or frequency of immunogen-specific T cells or the total number and/or frequency of T cells may be reduced in the presence of a CD40 inhibitor as compared to when the CD40 inhibitor is absent. Without wishing to be bound by theory, the mechanism of action of inhibition of an immune response comprising suppression of a T cell response to an immunogen may comprise, e.g., inhibition of antigen presenting cell (APC) licensing, including licensing of dendritic cells (DCs), macrophages, and B cells. CD40 can be expressed on antigen

presentation cells (APCs), and CD40L-CD40 interactions between CD4+ T cells and APCs can lead to so-called "licensing" of APCs. APC licensing, especially for dendritic cells (DCs), can enhance their antigen presentation functions and further promote T cell responses, including cytotoxic CD8+ T cell responses. Licensing can also render macrophages more effective killers of pathogens. If DCs are not as mature due to CD40 signaling blockade of licensing, they can default to a more tolerogenic priming state, e.g. they may tolerize T cells instead of activating them. The general mechanism of action can, in some ways, parallel other methods of co-stimulation blockade (e.g. CTLA4-Ig/belatacept/abatacept), which also attempt to block co-stimulation signals to promote tolerogenic priming. If an initial response to a transgene or recombinant protein is blocked, then the gradual exposure to the transgene protein (or protein therapeutic) afterwards may be less immunogenic than if the immune system were exposed all at once. The consequences could be that CD40 blockade may be used more transiently in one or a few doses (rather than repeated administrations or continuous exposure) to prevent long-term immunogenicity to transgene or to immunogenic protein therapeutics. Put another way, the distinction may be preventing responses versus programming the immune system to accept a foreign protein as self.

[01047] In some embodiments, the number and/or frequency of immunogen-specific T cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The number and/or frequency of immunogen-specific T cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The number and/or frequency of immunogen-specific T cells may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01048] In some embodiments, the total number and/or frequency of T cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about

25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The total number and/or frequency of T cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The total number and/or frequency of T cells may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01049] In some embodiments, T cell proliferation and/or activation is reduced in the presence of a CD40 inhibitor described herein as compared to when the CD40 inhibitor is absent. In some embodiments, T cell proliferation and/or activation may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. T cell proliferation and/or activation may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. T cell proliferation and/or activation may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01050] In some embodiments, the T cell can be a CD4+ T cell, for example, a CD4+ Ki-67+ T cell.

[01051] In some embodiments, the T cell can be a T Follicular Helper cell (TFH cell).

[01052] In some embodiments, the T cell can be a regulatory T cells (Treg).

[01053] In some embodiments, the inhibition of an immune response may comprise suppression of an immunogen-specific IFNγ response. In some embodiments, an immunogen-specific IFNγ response is reduced in the presence of a CD40 inhibitor as compared to when the

CD40 inhibitor is absent. In some embodiments, an immunogen-specific IFNγ response may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. An immunogen-specific IFNγ response may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. An immunogen-specific IFNγ response may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01054] In some embodiments, the inhibition of an immune response may comprise suppression of an immunogen-specific IgG and/or IgM response. In some embodiments, an immunogen-specific IgG and/or IgM response is reduced in the presence of a CD40 inhibitor as compared to when the CD40 inhibitor is absent. In some embodiments, an immunogen-specific IgG and/or IgM response may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. An immunogen-specific IgG and/or IgM response may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. An immunogen-specific IgG and/or IgM response may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01055] In one aspect, the present disclosure provides a method for inhibiting generation of neutralizing antibodies (nAbs) to an immunogen in a subject in need thereof, the method

comprising administering to the subject an effective amount of a CD40 inhibitor. As a non-limiting example, the generation of neutralizing antibodies to an immunogen may be inhibited by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The generation of neutralizing antibodies to an immunogen be inhibited by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The generation of neutralizing antibodies to an immunogen may be inhibited by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%, or more.

[01056] In another aspect, provided herein is a method for preventing and/or suppressing an immunogen-specific T cell response in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor. In another aspect, provided herein is a method for preventing and/or suppressing an immunogen-specific T cell response in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

[01057] As a non-limiting example, the prevention and/or suppression of an immunogen-specific T cell response may be inhibited by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The prevention and/or suppression of an immunogen-specific T cell response may be inhibited by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The prevention and/or suppression of an immunogen-specific T cell response may be inhibited by about 50%, about 55%, about 60%,

about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%, or more.

[01058] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises suppression of numbers and/or frequencies of the immunogen-specific T cells.

[01059] In some embodiments, the numbers and/or frequencies of the immunogen-specific T cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The numbers and/or frequencies of the immunogen-specific T cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The numbers and/or frequencies of the immunogen-specific T cells may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01060] In some embodiments, the immunogen-specific T cells comprise follicular T helper cells (TFH) and/or CD4+ T cells.

[01061] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or a tissue in the subject in response to the immunogen.

[01062] In some embodiments, the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle, and the prevention and/or suppression of the immunogen-specific T cell response comprises increasing or maintaining the level of transgene expression in the subject.

[01063] In some embodiments, the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or tissue in the subject in response to transgene expression in the organ and/or a tissue.

[01064] In some embodiments, the tissue is muscle. Non-limiting tissues include adipose tissue, blood/bone marrow, bone/cartilage/joint, brain/spinal cord/cns/bbb, breast, colon, esophagus, eye, heart, kidney, liver, lung/bronchus, lymph node, ovary, pancreas, pbmc, peripheral nervous system, placenta, prostate, rectum, skeletal muscle, skin, small intestine, spleen, stomach, testis, and uterus.

[01065] In some embodiments, the organ is liver. Non-limiting organs include the central nervous system (CNS), the peripheral nervous system (PNS), lungs, liver, bone, skeletal and cardiac muscle, and the reticuloendothelial system.

[01066] In one aspect, the present disclosure provides a method for increasing effectiveness of re-administration of an immunogen to a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor. As a non-limiting example, the effectiveness of re-administration of an immunogen may be increased by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The effectiveness of re-administration of an immunogen be increased by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The effectiveness of re-administration of an immunogen may be increased by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01067] In some embodiments, the immunogen re-administration occurs via the same administration route as its prior administration. In some embodiments, the immunogen re-administration occurs via a different administration route than its prior administration. In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject. In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject. In some embodiments, non-neutralizing antibodies may impact the transduction pattern of AAVs and/or the biodistribution/uptake of proteins or transgenes. In some embodiments, the CD40 inhibitor is administered before the administration of the immunogen. In some embodiments, the CD40 inhibitor is administered simultaneously

with the administration of the immunogen. In some embodiments, the CD40 inhibitor is administered after the administration of the immunogen. In some embodiments, the immunogen is administered two or more times and the CD40 inhibitor is administered before and/or between each of the administrations of the immunogen. In some embodiments, the immunogen is an immunogenic delivery vehicle, a polypeptide, a polynucleotide, a glycan, or a lipid. In some embodiments, the immunogen is an immunogenic delivery vehicle or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

Viral particles

[01068] In one aspect, the present disclosure provides for methods for inhibiting an immune response to a viral vector in a subject in need thereof, the method comprising administering to the subject an effective amount of a CD40 inhibitor, e.g., an antigen-binding molecule of the present disclosure such as a monospecific, bispecific, or multispecific antibody, that specifically binds to CD40, or an antigen-binding fragment thereof. The terms "viral vector" and "viral particle" can be used synonymously and interchangeably herein.

[01069] In some embodiments, the CD40 inhibitor is capable of inhibiting an immune response which can be elicited by a viral particle, or a portion thereof (e.g., a capsid protein). In some embodiments, the viral particle can comprise a viral vector (e.g., an adeno-associated virus (AAV) vector, an adenovirus vector, a retrovirus vector, or an oncolytic virus vector) which can comprise one or more of a heterologous and/or recombinant nucleotide sequence(s) of interest (e.g., a nucleotide sequence encoding a gene, or portion thereof, desired to be expressed in a cell targeted by the viral particle (e.g., a transgene), which nucleotide sequence of interest may be, e.g., DNA or RNA). In some embodiments, the nucleotide sequence can encode a polypeptide of interest disclosed herein. In various embodiments, the nucleotide sequence can encode a transgene product comprising one or more therapeutic agents (e.g., therapeutic proteins or polypeptides) described herein. In some embodiments, the nucleotide sequence encodes a therapeutic protein, a suicide gene, an antibody or a fragment thereof, an antisense oligonucleotide, a ribozyme, an RNAi molecule, and/or a shRNA molecule. In some embodiments, the nucleotide sequence may encode a growth factor, a neurotrophic factor, a disease modifying muscle protein, and/or a metabolic protein, e.g., for muscle atrophy conditions or metabolic diseases.

[01070] In some embodiments, the CD40 inhibitor described herein is capable of inhibiting an immune response which can be elicited by a vector, e.g., viral vector, or a portion thereof, e.g., an adenovirus-associated virus (AAV) vector.

[01071] A vector can comprise additional sequences such as, for example, replication origins, promoters, and genes encoding antibiotic resistance. Some vectors may be circular. Alternatively, the vector may be linear. The vector can be in the packaged for delivered via a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid. Non-limiting exemplary vectors include plasmids, phagemids, cosmids, artificial chromosomes, minichromosomes, transposons, viral vectors, and expression vectors.

[01072] Some vectors may be circular. Alternatively, the vector may be linear. The vector can be packaged for delivered via a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid. Non-limiting exemplary vectors include plasmids, phagemids, cosmids, artificial chromosomes, minichromosomes, transposons, viral vectors, and expression vectors.

[01073] The vectors can be, for example, viral vectors such as adeno-associated virus (AAV) vectors. The AAV may be any suitable serotype and may be a single-stranded AAV (ssAAV) or a self-complementary AAV (scAAV). Other exemplary viruses/viral vectors include retroviruses, lentiviruses, adenoviruses, vaccinia viruses, poxviruses, and herpes simplex viruses. The viruses can infect dividing cells, non-dividing cells, or both dividing and non-dividing cells. The viruses can integrate into the host genome or alternatively do not integrate into the host genome. Such viruses can also be engineered to have reduced immunity. The viruses can be replication-competent or can be replication-defective (e.g., defective in one or more genes necessary for additional rounds of virion replication and/or packaging). Viruses can cause transient expression or longer-lasting expression. Viral vector may be genetically modified from their wild type counterparts. For example, the viral vector may comprise an insertion, deletion, or substitution of one or more nucleotides to facilitate cloning or such that one or more properties of the vector is changed. Such properties may include packaging capacity, transduction efficiency, immunogenicity, genome integration, replication, transcription, and translation. In some examples, a portion of the viral genome may be deleted such that the virus is capable of packaging exogenous sequences having a larger size. In some examples, the viral vector may have an enhanced transduction efficiency. In some examples, the immune response induced by the virus in a host may be reduced. In some examples, viral genes (such as integrase) that promote integration of the viral sequence into a host genome may be mutated such that the virus becomes non-integrating. In some examples, the viral vector may be replication defective. In some examples, the viral vector may comprise exogenous transcriptional or translational control sequences to drive expression of coding sequences on the vector. In some examples, the virus may be helper-dependent. For example, the virus may need one or more helper virus to supply viral components (such as viral proteins) required to

amplify and package the vectors into viral particles. In such a case, one or more helper components, including one or more vectors encoding the viral components, may be introduced into a host cell or population of host cells along with the vector system described herein. In other examples, the virus may be helper-free. For example, the virus may be capable of amplifying and packaging the vectors without a helper virus. In some examples, the vector system described herein may also encode the viral components required for virus amplification and packaging.

[01074] Introduction of nucleic acids can also be accomplished by virus-mediated delivery, such as AAV-mediated delivery or lentivirus-mediated delivery. The vectors can be, for example, viral vectors such as adeno-associated virus (AAV) vectors. The AAV may be any suitable serotype and may be a single-stranded AAV (ssAAV) or a self-complementary AAV (scAAV). Other exemplary viruses/viral vectors include retroviruses, lentiviruses, adenoviruses, vaccinia viruses, poxviruses, and herpes simplex viruses. The viruses can infect dividing cells, non-dividing cells, or both dividing and non-dividing cells. The viruses can integrate into the host genome or alternatively do not integrate into the host genome. Such viruses can also be engineered to have reduced immunity. The viruses can be replication-competent or can be replication-defective (e.g., defective in one or more genes necessary for additional rounds of virion replication and/or packaging). Viral vector may be genetically modified from their wild type counterparts. For example, the viral vector may comprise an insertion, deletion, or substitution of one or more nucleotides to facilitate cloning or such that one or more properties of the vector is changed. Such properties may include packaging capacity, transduction efficiency, immunogenicity, genome integration, replication, transcription, and translation. In some examples, a portion of the viral genome may be deleted such that the virus is capable of packaging exogenous sequences having a larger size. In some examples, the viral vector may have an enhanced transduction efficiency. In some examples, the immune response induced by the virus in a host may be reduced. In some examples, viral genes (such as integrase) that promote integration of the viral sequence into a host genome may be mutated such that the virus becomes non-integrating. In some examples, the viral vector may be replication defective. In some examples, the viral vector may comprise exogenous transcriptional or translational control sequences to drive expression of coding sequences on the vector. In some examples, the virus may be helper-dependent. For example, the virus may need one or more helper virus to supply viral components (such as viral proteins) required to amplify and package the vectors into viral particles. In such a case, one or more helper components, including one or more vectors encoding the viral components, may be introduced into a host cell or population of host

cells along with the vector system described herein. In other examples, the virus may be helper-free. For example, the virus may be capable of amplifying and packaging the vectors without a helper virus. In some examples, the vector system described herein may also encode the viral components required for virus amplification and packaging

[01075] Exemplary viral titers (e.g., AAV titers) include 10^{12}, 10^{13}, 10^{14}, 10^{15}, and 10^{16} vector genomes/mL. Exemplary viral titers (e.g., AAV titers) include about 10^{12}, about 10^{13}, about 10^{14}, about 10^{15}, and about 10^{16} vector genomes (vg)/mL, or between about 10^{12} to about 10^{16}, between about 10^{12} to about 10^{15}, between about 10^{12} to about 10^{14}, between about 10^{12} to about 10^{13}, between about 10^{13} to about 10^{16}, between about 10^{14} to about 10^{16}, between about 10^{15} to about 10^{16}, or between about 10^{13} to about 10^{15} vg/mL. Other exemplary viral titers (e.g., AAV titers) include about 10^{12}, about 10^{13}, about 10^{14}, about 10^{15}, and about 10^{16} vector genomes (vg)/kg of body weight, or between about 10^{12} to about 10^{16}, between about 10^{12} to about 10^{15}, between about 10^{12} to about 10^{14}, between about 10^{12} to about 10^{13}, between about 10^{13} to about 10^{16}, between about 10^{14} to about 10^{16}, between about 10^{15} to about 10^{16}, or between about 10^{13} to about 10^{15} vg/kg of body weight. In one example, the viral titer is between about 10^{13} to about 10^{14} vg/mL or vg/kg. In another example, the viral titer is between about 10^{12} to about 10^{13} vg/mL or vg/kg (e.g., between about 10^{12} to about 10^{13} vg/kg). In another example, the viral titer is between about 10^{12} to about 10^{14} vg/mL or vg/kg (e.g., between about 10^{12} to about 10^{14} vg/kg). For example, the viral titer can be between about 1.5E12 to about 1.5E13 vg/kg, can be about 1.5E12 vg/kg, or can be about 1.5E13 vg/kg. In another example, the viral titer is about 2E13 vg/mL or vg/kg. In another example, the viral titer is about 1E12 to about 2E14 vg/kg. In another example, the viral titer is about 3E11 vg/kg to about 5E13 vg/kg. In some embodiments, the viral titer is about 1E13 vg/kg.

[01076] Viral vectors can be derived from naturally occurring virus genomes, which typically are modified to be replication incompetent, e.g. non-replicating. Non-replicating viruses require the provision of proteins in trans for replication. Typically, those proteins are stably or transiently expressed in a viral producer cell line, thereby allowing replication of the virus. The viral vectors are, thus, typically infectious and non-replicating. Non-limiting examples of viral vectors include adenovirus vectors, adeno-associated virus (AAV) vectors (e.g., AAV type 8), alphavirus vectors (e.g., Venezuelan equine encephalitis virus (VEE), Sindbis virus (SIN), Semliki forest virus (SFV), and VEE-SIN chimeras), herpes virus vectors (e.g., vectors derived from cytomegaloviruses, like rhesus cytomegalovirus (RhCMV)), arena virus vectors (e.g. lymphocytic choriomeningitis virus (LCMV) vectors), measles virus vectors, pox virus vectors (e.g., vaccinia virus, modified vaccinia virus Ankara (MVA), NYVAC (derived from the

Copenhagen strain of vaccinia), and avipox vectors (canarypox (ALVAC) and fowlpox (FPV) vectors), vesicular stomatitis virus (VSV) vectors, retrovirus vectors, lentivirus vectors, simian virus 40 (SV40), bovine papilloma viruses, Epstein-Barr viruses, Moloney murine leukemia viruses, Harvey murine sarcoma viruses, murine mammary tumor viruses, Rous sarcoma viruses, poxvirus viral like particles, baculoviral vectors and bacterial spores.

[01077] Adeno-associated viruses (AAVs) are endemic in multiple species including human and non-human primates (NHPs). At least 12 natural serotypes and hundreds of natural variants have been isolated and characterized to date. *See, e.g.*, Li et al. (2020) *Nat. Rev. Genet.* 21:255-272, herein incorporated by reference in its entirety for all purposes. AAV particles are naturally composed of a non-enveloped icosahedral protein capsid containing a single-stranded DNA (ssDNA) genome. The DNA genome is flanked by two inverted terminal repeats (ITRs) which serve as the viral origins of replication and packaging signals. The *rep* gene encodes four proteins required for viral replication and packaging whilst the *cap* gene encodes the three structural capsid subunits which dictate the AAV serotype, and the Assembly Activating Protein (AAP) which promotes virion assembly in some serotypes.

[01078] Recombinant AAV (rAAV) is currently one of the most commonly used viral vectors used in gene therapy to treat human diseases by delivering therapeutic transgenes to target cells *in vivo*. Indeed, rAAV vectors are composed of icosahedral capsids similar to natural AAVs, but rAAV virions do not encapsidate AAV protein-coding or AAV replicating sequences. These viral vectors are non-replicating. The only viral sequences required in rAAV vectors are the two ITRs, which are needed to guide genome replication and packaging during manufacturing of the rAAV vector. rAAV genomes are devoid of AAV *rep* and *cap* genes, rendering them non-replicating *in vivo*. rAAV vectors are produced by expressing *rep* and *cap* genes along with additional viral helper proteins *in trans*, in combination with the intended transgene cassette flanked by AAV ITRs.

[01079] In therapeutic rAAV genomes, a gene expression cassette is placed between ITR sequences. Typically, rAAV genome cassettes comprise of a promoter to drive expression of a therapeutic transgene, followed by polyadenylation sequence. The ITRs flanking a rAAV expression cassette can be derived from AAV2, the first serotype to be isolated and converted into a recombinant viral vector. Since then, most rAAV production methods rely on AAV2 *Rep*-based packaging systems. *See, e.g.*, Colella et al. (2017) *Mol. Ther. Methods Clin. Dev.* 8:87-104, herein incorporated by reference in its entirety for all purposes.

[01080] The specific serotype of a recombinant AAV vector influences it's *in vivo* tropism to specific tissues. AAV capsid proteins are responsible for mediating attachment and entry into

target cells, followed by endosomal escape and trafficking to the nucleus. Thus, the choice of serotype when developing a rAAV vector will influence what cell types and tissues the vector is most likely to bind to and transduce when injected *in vivo*. Several serotypes of rAAVs, including rAAV8, are capable of transducing the liver when delivered systemically in mice, NHPs (e.g., cynomolgus macaques), and humans. *See, e.g.*, Li et al. (2020) *Nat. Rev. Genet.* 21:255-272, herein incorporated by reference in its entirety for all purposes.

[01081] Once in the nucleus, the ssDNA genome is released from the virion and a complementary DNA strand is synthesized to generate a double-stranded DNA (dsDNA) molecule. Double-stranded AAV genomes naturally circularize via their ITRs and become episomes which will persist extrachromosomally in the nucleus. Therefore, for episomal gene therapy programs, rAAV-delivered rAAV episomes provide long-term, promoter-driven gene expression in non-dividing cells. However, this rAAV-delivered episomal DNA is diluted out as cells divide.

[01082] The ssDNA AAV genome consists of two open reading frames, Rep and Cap, flanked by two inverted terminal repeats that allow for synthesis of the complementary DNA strand. When constructing an AAV transfer plasmid, the transgene is placed between the two ITRs, and Rep and Cap can be supplied *in trans*. In addition to Rep and Cap, AAV can require a helper plasmid containing genes from adenovirus. These genes (E4, E2a, and VA) mediate AAV replication. For example, the transfer plasmid, Rep/Cap, and the helper plasmid can be transfected into HEK293 cells containing the adenovirus gene E1+ to produce infectious AAV particles. Alternatively, the Rep, Cap, and adenovirus helper genes may be combined into a single plasmid. Similar packaging cells and methods can be used for other viruses, such as retroviruses.

[01083] Multiple serotypes of AAV have been identified. These serotypes differ in the types of cells they infect (i.e., their tropism), allowing preferential transduction of specific cell types. The term AAV includes, for example, AAV1, AAV2, AAV3, AAV3B, AAV4, AAV5, AAV6, AAV6.2, AAV7, AAVrh.64R1, AAVhu.37, AAVrh.8, AAVrh.32.33, AAV8, AAV9, AAV-DJ, AAV2/8, AAVrh10, AAVLK03, AV10, AAV11, AAV12, rh10, and hybrids thereof, avian AAV, bovine AAV, canine AAV, equine AAV, primate AAV, non-primate AAV, and ovine AAV. The genomic sequences of various serotypes of AAV, as well as the sequences of the native terminal repeats (TRs), Rep proteins, and capsid subunits are known in the art. Such sequences may be found in the literature or in public databases such as GenBank. An “AAV vector” as used herein refers to an AAV vector comprising a heterologous sequence not of AAV origin (i.e., a nucleic acid sequence heterologous to AAV), typically comprising a sequence encoding an exogenous

polypeptide of interest. The construct may comprise an AAV1, AAV2, AAV3, AAV3B, AAV4, AAV5, AAV6, AAV6.2, AAV7, AAVrh.64R1, AAVhu.37, AAVrh.8, AAVrh.32.33, AAV8, AAV9, AAV-DJ, AAV2/8, AAVrh10, AAVLK03, AV10, AAV11, AAV12, rh10, and hybrids thereof, avian AAV, bovine AAV, canine AAV, equine AAV, primate AAV, non-primate AAV, and ovine AAV capsid sequence. In general, the heterologous nucleic acid sequence (the transgene) is flanked by at least one, and generally by two, AAV inverted terminal repeat sequences (ITRs). An AAV vector may either be single-stranded (ssAAV) or self-complementary (scAAV). Examples of serotypes for liver tissue include AAV3B, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh.74, and AAVhu.37, and particularly AAV8. In a specific example, the AAV vector comprising the nucleic acid construct can be recombinant AAV8 (rAAV8). A rAAV8 vector as described herein is one in which the capsid is from AAV8. For example, an AAV vector using ITRs from AAV2 and a capsid of AAV8 is considered herein to be a rAAV8 vector.

[01084] Tropism can be further refined through pseudotyping, which is the mixing of a capsid and a genome from different viral serotypes. For example AAV2/5 indicates a virus containing the genome of serotype 2 packaged in the capsid from serotype 5. Use of pseudotyped viruses can improve transduction efficiency, as well as alter tropism. Hybrid capsids derived from different serotypes can also be used to alter viral tropism. For example, AAV-DJ contains a hybrid capsid from eight serotypes and displays high infectivity across a broad range of cell types *in vivo*. AAV-DJ8 is another example that displays the properties of AAV-DJ but with enhanced brain uptake. AAV serotypes can also be modified through mutations. Examples of mutational modifications of AAV2 include Y444F, Y500F, Y730F, and S662V. Examples of mutational modifications of AAV3 include Y705F, Y731F, and T492V. Examples of mutational modifications of AAV6 include S663V and T492V. Other pseudotyped/modified AAV variants include AAV2/1, AAV2/6, AAV2/7, AAV2/8, AAV2/9, AAV2.5, AAV8.2, and AAV/SASTG.

[01085] To accelerate transgene expression, self-complementary AAV (scAAV) variants can be used. Because AAV depends on the cell's DNA replication machinery to synthesize the complementary strand of the AAV's single-stranded DNA genome, transgene expression may be delayed. To address this delay, scAAV containing complementary sequences that are capable of spontaneously annealing upon infection can be used, eliminating the requirement for host cell DNA synthesis. However, single-stranded AAV (ssAAV) vectors can also be used.

[01086] To increase packaging capacity, longer transgenes may be split between two AAV transfer plasmids, the first with a 3' splice donor and the second with a 5' splice acceptor. Upon co-infection of a cell, these viruses form concatemers, are spliced together, and the full-length transgene can be expressed. Although this allows for longer transgene expression, expression

is less efficient. Similar methods for increasing capacity utilize homologous recombination. For example, a transgene can be divided between two transfer plasmids but with substantial sequence overlap such that co-expression induces homologous recombination and expression of the full-length transgene.

[01087] As further examples, adenovirus vectors may be derived from human adenovirus (Ad) but also from adenoviruses that infect other species, such as bovine adenovirus (e.g. bovine adenovirus 3, BAdV3), canine adenovirus (e.g. CAdV2), porcine adenovirus (e.g. PAdV3 or 5), or adenoviruses that infect great apes, such as Chimpanzee (Pan), Gorilla (Gorilla), Orangutan (Pongo), Bonobo (Pan paniscus) and common chimpanzee (Pan troglodytes). Poxvirus (Poxviridae) vectors may be derived from smallpox virus (variola), vaccinia virus, cowpox virus or monkeypox virus. Exemplary vaccinia viruses are the Copenhagen vaccinia virus (W), New York Attenuated Vaccinia Virus (NYVAC), ALVAC, TROVAC and Modified Vaccinia Ankara (MVA).

[01088] In some embodiments, a CD40 inhibitor of the present disclosure may inhibit an immune response which may be elicited by a transgene product, e.g., a transgene product (e.g., a therapeutic polypeptide or polynucleotide of interest or disclosed herein which is encoded by the transgene) comprising one or more therapeutic agents. The one or more therapeutic agents may comprise a therapeutic protein (e.g., a therapeutic polypeptide) and/or a therapeutic nucleic acid. Non-limiting examples of therapeutic agents which may be expressed by a transgene using methods of the present disclosure include, e.g., proteins and polypeptides, antisense RNA, or ribozymes, or any combination thereof. In some embodiments, the heterologous and/or recombinant nucleotide sequence becomes integrated into the cell genome. In some embodiments, the heterologous and/or recombinant nucleotide sequence does not become integrated into the cell genome.

[01089] Examples of therapeutic proteins and polypeptides suitable for expression methods of the present disclosure include human hormones such as growth hormone, prolactin, insulin, luteinizing hormone, calcitonin, follicle stimulating hormone, chorionic gonadotropin or thyroid stimulating hormone; a chemokine including, MIP-1β and RANTES Iα; a colony stimulating factor, e.g., G-CSF, GM- M-CSF and CSF; growth factors such as IGF-1 and IGF-2; a cytokine, such as interleukin (IL)-1, IL-2 IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14 and IL-15, α-interferons, β-interferons, the γ-interferons, LFA-1, tumor necrosis factor, CD3, ICAM-1 and LFA-3; LDL receptor, ornithine transcarbamylase, phenylalanine hydroxylase, and αl-antitrypsin.

[01090] Additional examples of sequences expressible using the methods described herein include sequences of Protein S and Gas6, thrombin, acidic fibroblast growth factor (FGF-1), basic FGF (FGF-2), keratinocyte growth factor (KGF), TGF, platelet derived growth factor (PDGF), epidermal growth factor (EGF), hepatocyte growth factor (HGF) and HGF activators, PSA, nerve cell growth factor (NCGF), glial cell derived nerve growth factor (GDNF), vascular endothelial growth factor (VEGF), Arg-vasopressin, thyroid hormones asoxymethane, triodothyronine, LIF, amphiregulin, soluble thrombomodulin, stem cell factor, osteogenic protein 1, the bone morphogenic proteins, MFG, MGSA, heregulins and melanotropin, human growth hormone, leptin, IL-2, erythropoietin, and thrombopoietin (G-CSF).

[01091] In some embodiments, vectors and/or viral particles described herein may comprise, e.g., genes encoding apoptotic factors, genes encoding cytotoxic molecules, genes encoding anti-apoptotic factors, genes encoding immune-stimulatory molecules, a TNF-α gene, a p53 gene, interferon genes, "suicide genes" (i.e., the genes which cause a cell to kill itself through apoptosis; non-limiting examples of suicide genes include, e.g., herpes simplex virus thymidine kinase (HSV-TK), which converts ganciclovir (GCV) into cytotoxic compounds, *Escherichia coli* cytosine deaminase, which allows the formation of a cytotoxic chemotherapeutic agent from a non-toxic precursor, Varicella-zoster virus thymidine kinase, deoxycytidine kinase, purine nucleoside phosphorylase, nitroreductase, β-galactosidase, hepatic cytochrome P450-2B1, linamarase, horseradish peroxidase, and carboxypeptidase).

[01092] In some embodiments, a protein or polypeptide encoded by the genes inserted into the vectors and viral particles of the present disclosure can provide one or more antigens or antigenically active fragments thereof associated with, e.g., one or more infectious agents such as a bacteria, virus, parasite, or fungus, or a combination thereof, which may be used to immunize a subject. An active fragment described herein may comprise a polypeptide which contains less than a full-length sequence but that retains sufficient biological activity to be used in the methods of the disclosure.

[01093] As a non-limiting example, antigens can include *H. Pylori* antigens VacA (cytotoxin), heat shock protein, CagA (cai antigen) and urease B and HCV antigens, such as HCV NS3, NS4, El, E2 and/or E2a. In some embodiments, an antigen can include influenza antigens, rabies antigens and bacterial antigens from *Bordetella pertussia*, *Neiserria meningitides* (A, B, C, Y 135), gD, gB and other glycoproteins, HSV (herpes simplex virus), MMR and VZV (Varicella Zoster virus) antigens, CMV (cytomegalovirus) gB or gH glycoproteins, hepatitis D virus (HDV) delta antigen HIV gp 120, p24 and other proteins, hepatitis A virus (HAV) antigens, and EBV (Epstein Barr vims).

[01094] In some embodiments, a protein or polypeptide encoded by heterologous or recombinant nucleotide sequence(s) inserted into the vectors and viral particles of the present disclosure can provide one or more antigen-binding molecules or antigen-binding fragments thereof, e.g., antibodies or antigen-binding fragments thereof. Antibodies or antigen-binding fragments thereof encompass derivatives, functional equivalents, and homologues of antibodies, humanized antibodies, including any polypeptide comprising an immunoglobulin binding domain, whether natural or wholly or partially synthetic and any polypeptide or protein having a binding domain which is, or is homologous to, an antibody binding domain. Chimeric molecules comprising an immunoglobulin binding domain, or equivalent, fused to another polypeptide are therefore included. A humanized antibody may be a modified antibody having the variable regions of a non-human, e.g. murine, antibody, and the constant region of a human antibody. Examples of antibodies are the immunoglobulin isotypes (e.g., IgG, IgE, IgM, IgD and IgA) and their isotypic subclasses; or fragments that comprise an antigen binding domain such as Fab, scFv, Fv, dAb, Fd; and diabodies. Antibodies may be polyclonal or monoclonal. A monoclonal antibody may be referred to herein as "mAb". In some embodiments, the antibody is a multispecific antibody. In some embodiments, the antibody is a bispecific antibody. The bispecific antibody may comprise a second targeting moiety that targets to the desired cell or tissue, e.g., liver, or to another desired antigen associated with the same or similar disease or disorder (e.g., liver cancer antigen).

[01095] In some embodiments, an antigen-binding molecule or antigen-binding fragment thereof (e.g., an scFv) may be fused to a payload such as, e.g., an alpha-glucosidase polypeptide (GAA) or a arylsulfatase B (ARSB) polypeptide, or variants thereof, to form an antigen-binding molecule:payload fusion protein. The term "fused" with regard to fused polypeptides refers to polypeptides joined directly or indirectly (e.g., via a linker or other polypeptide).

[01096] An antisense sequence that can be expressed by the vectors and viral particles of the present disclosure can be an RNA sequence which is capable of preventing or limiting the expression of defective, over-produced, or otherwise undesirable molecules by being sufficiently complementary to a target sequence. In some embodiments, the target sequence may comprise an mRNA that encodes a protein, and the antisense RNA can bind to the mRNA and prevent its translation. In some embodiments, the target sequence can be a portion of a gene that is requisite for transcription, and the antisense RNA can bind to the gene portion and prevent or limit its transcription.

[01097] In certain embodiments, the antisense sequence is an antisense oligonucleotide (ASO). An ASO can down regulate a target by inducing RNase H endonuclease cleavage of a target RNA, by steric hindrance of ribosomal activity, by inhibiting 5′ cap formation, or by altering splicing. An ASO can be, but is not limited to, a gapmer or a morpholino. An antisense oligonucleotide typically comprises a short nucleotide sequence which is substantially complementary to a target nucleotide sequence in a pre-mRNA molecule, heterogeneous nuclear RNA (hnRNA) or mRNA molecule. The degree of complementarity (or substantial complementarity) of the antisense sequence is preferably such that a molecule comprising the antisense sequence can form a stable double stranded hybrid with the target nucleotide sequence in the RNA molecule under physiological conditions. Antisense oligonucleotides are often synthetic and chemically modified.

[01098] In some embodiments, the vectors and viral particles of the present disclosure can express a ribozyme (ribonucleic acid enzyme). A ribozyme is a molecule, commonly an RNA molecule, that is capable of performing specific biochemical reactions, akin to the action of protein enzymes. Ribozymes comprise molecules possessing catalytic activities such as, but not limited to, the capacity to cleave at specific phosphodiester linkages in RNA molecules to which they have hybridized, e.g., RNA-containing substrates, lncRNAs, mRNAs, and ribozymes. Exemplary ribozymes include ribozymes to, e.g., hepatitis A, hepatitis B and hepatitis C.

[01099] In some embodiments, the CD40 inhibitor of the present disclosure may inhibit an immune response via blocking and/or suppressing induced and/or pre-existing immunity of a host (e.g., a subject) against a viral particle or portion thereof, and/or a gene delivery vector (e.g., a viral vector such as a AAV vector), or a transgene product thereof, described herein. In some embodiments, the induced and/or pre-existing host immunity may comprise, e.g., B cell production of at least one neutralizing antibody (nAb) to a viral particle or portion thereof, e.g., capsid protein, and/or a viral vector described herein. An immune response involving production of nAbs induced by viral particles and/or vectors can be associated with T cell and B cell activation.

[01100] A neutralizing antibody (nAb) may be capable of both binding and neutralizing a viral particle or a portion thereof. In some embodiments, neutralizing (or neutralize or neutralization and the like) in the context of the present disclosure may comprise an effect of immunoglobulins, such as antibodies generated in a host immune response, in reducing the efficacy and/or delivery of a viral particle. As an example, neutralization by an at least one nAb described herein may be realized such that the nAb is directed to the viral particle surface (e.g., capsid protein) which may result in aggregation of viral particles and/or may be realized by

inhibition of the fusion of viral and a cellular membrane(s) after attachment of the viral particle to a target cell, by inhibition of endocytosis, and/or by inhibition of production of viral progeny. In various embodiments, an antibody generated in a subject's host immune response can play a neutralizing role thereby causing the delivery effectiveness of the viral particle to be reduced or eliminated. In some embodiments, the induced and/or preexisting host immunity may comprise B and/or T cell immune responses described herein. The blockade and/or suppression of induced and/or preexisting host immunity against viral particles or portions thereof, can improve viral transduction and allow for effective re-administration (i.e., re-dosing) of the viral particles during gene therapy.

[01101] In some embodiments, the methods for inhibiting an immune response described herein may be useful when a subject has or will develop an immune response to one or more viral particles, or portion thereof (e.g., an immune response comprising generation of nAbs), e.g., one or more AAV vector particles comprising a gene or portion thereof contained within the AAV vector which may encode a transgene product comprising one or more therapeutic agent(s), e.g., as part of a gene therapy regimen. In particular, the present disclosure is useful when a subject in need of a therapeutic agent may require multiple or extended treatments, e.g., over a period of years. In some embodiments, the present disclosure allows for multiple administrations (i.e., re-dosing) to the same subject of the same recombinant AAV particles which may have a gene encoding a therapeutic agent needed by the subject, and provides for expression of the therapeutic agent even when a subject has developed an immunity to the AAV of the vector particle. In some embodiments, the present disclosure can be useful for a subject in need of a therapeutic protein that would require and/or benefit from a therapeutic agent on a continuous or bolus basis.

[01102] In one aspect, the present disclosure provides for methods for inhibiting generation of neutralizing antibodies (nAbs) to, e.g., a viral particle and/or a viral vector described herein, or a portion thereof, in a subject in need thereof, the method comprising administering to the subject an effective amount of a CD40 inhibitor described herein.

[01103] In another aspect, the present disclosure provides for methods for increasing or maintaining the level of a transgene expression in a subject in need thereof, the method comprising administering to the subject an effective amount of an in CD40 inhibitor.

[01104] In yet another aspect, the present disclosure provides for methods for increasing effectiveness of re-administration of a viral vector of the same or similar viral origin as the originally administered viral vector in a subject in need thereof, the methods comprising administering to the subject an effective amount of a CD40 inhibitor.

[01105] In some embodiments, the present disclosure contemplates a method for increasing effectiveness of administration of a subsequently administered viral vector following administration of an originally administered viral vector in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor, and the subsequently administered viral vector is of the same or similar viral origin as the originally administered viral vector. In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject. In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[01106] The viral particles and/or vectors described herein can be derived from any enveloped or non-enveloped virus. Non-limiting examples of enveloped viruses from which the viral particles and/or viral vectors described herein can be derived include, e.g., retroviruses (e.g., rous sarcoma virus, human and bovine T-cell leukemia virus (HTLV and BLV)), lentiviruses (e.g., human and simian immunodeficiency viruses (HIV and SIV), Mason-Pfizer monkey virus), foamy viruses (e.g., Human Foamy Virus (HFV)), herpes viruses (herpes simplex virus (HSV), varicella-zoster virus, VZVEBV, HCMV, HHV), hantaviruses, pox viruses (e.g., vertebrate and avian poxviruses, vaccinia viruses), orthomyxoviruses (e.g., influenza A, influenza B, influenza C viruses), paramyxoviruses (e.g., parainfluenza virus, respiratory syncytial virus, Sendai virus, mumps virus, measles and measles-like viruses), rhabdoviruses (e.g., vesicular stomatitis virus, rubella virus, rabies virus), coronaviruses (e.g., SARS, MERS), flaviviruses (e.g., Marburg virus, Reston virus, Ebola virus), alphaviruses (e.g., Sindbis virus), bunyaviruses, arenaviruses (e.g., LCMV, GTOV, JUNV, LASV, LUJV, MACV, SABV, WWAV), iridoviruses, and hepadnaviruses.

[01107] Non-limiting examples of non-enveloped viruses from which the viral particles and/or viral vectors described herein can be derived include, viruses from the families *Picornaviridae*, *Reoviridae*, *Caliciviridae*, *Adenoviridae* and *Parvoviridae*, such as calicivirus, picornavirus, astrovirus, adenovirus, reovirus, polyomavirus, papillomavirus, parvovirus (e.g., adeno-associated virus (AAV)), and type E Hepatitis virus. In some embodiments, the viral vectors are derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus. In some embodiments, the viral vectors are derived from AAV.

[01108] In some embodiments, the viral particles and/or vectors described herein can be derived from an oncolytic virus, including adenovirus, rhabdovirus, herpes virus, measles virus, coxsackievirus, poliovirus, reovirus, poxvirus, parvovirus, Maraba virus, Newcastle disease virus, or paramyxovirus, or any species or strain within these larger groups. A virus disclosed herein may be unaltered from the parental virus species (i.e., wild-type), or with gene modifications, e.g., gene additions.

[01109] In some embodiments, the viral particles and/or vectors described herein may be derived from a rhabdovirus. In some embodiments, the recombinant virus may comprise a rhabdovirus genome. The *Rhabdoviridae* family is mainly composed of a cage, bullet-shaped or bacilliform virus and has a negative-sense single-stranded RNA genome that infects vertebrates, invertebrates or plants. Non-limiting examples of rhabdoviruses that can be used in the present disclosure include rabies, cytolabudoviruses, dicholabdoviruses, ephemeraviruses, lyssaviruses, nobilabdoviruses, and vesiculoviruses. In some embodiments, the rhabdovirus is a vesiculovirus including, without limitation, a vesicular stomatitis virus (VSV)

[01110] In some embodiments, the viral particles and/or vectors described herein is derived from a virus of the family *Retroviridae*. In one specific embodiment, the viral particle described herein is a retroviral particle. In some embodiments, the viral particle is derived from a lentivirus. Compared to other gene transfer systems, lentiviral and retroviral vectors offer a wide range of advantages, including their ability to transduce a variety of cell types, to stably integrate transferred genetic material into the genome of the targeted host cell, and to express the transduced gene at significant levels. Vectors derived from the gamma-retroviruses, for example, the murine leukemia virus (MLV), have been used in clinical gene therapy trials (Ross et al., Hum. Gen Ther. 7:1781-1790, 1996).

[01111] In some embodiments, a viral particle described herein comprises one or more transfer vectors comprising a nucleotide sequence of interest. In some embodiments, the nucleotide sequence of interest is an RNA molecule transcribed by a transfer vector. In some embodiments a viral particle described herein comprises RNA comprising the nucleotide sequence of interest. In some embodiments, a viral particle as described herein comprises one or more transfer vectors, or one or more RNA molecule encoded by the transfer vector, wherein said transfer vector or RNA molecule comprises the nucleotide sequence of interest, and optionally, further comprises a viral element. In some embodiments, upon infection of a target cell with the viral particle, the nucleotide sequence of interest becomes integrated into the cell genome. In some embodiments, the at least one viral element is a retroviral element. In some embodiments, the at least one viral element is a lentiviral element. In some embodiments, the at least one viral element is a Psi (ψ) packaging signal. In some embodiments, in addition to a Psi (ψ) packaging signal, the viral element further comprises a 5' Long Terminal Repeat (LTR) and/or a 3' LTR, or a derivative or mutant thereof. In one specific embodiment, the at least one viral element is selected from the group consisting of a 5' Long Terminal Repeat (LTR), a Psi (ψ) packaging signal, a Rev Response Element (RRE), a promoter that drives expression of the nucleotide sequence of interest, a Central Polypurine Tract (cPPT), a Woodchuck hepatitis virus post-

transcriptional regulatory element (WPRE), a Unique 3' (U3), a Repeat (R) region, a Unique 5' (U5), a 3' LTR, a 3'LTR with the U3 element deleted (e.g., to make the lentivirus non-replicative), a Trans-activating response element (TAR), and any combination thereof.

[01112] In some embodiments, a viral particle described herein is designed such that a nucleotide of interest is integrated into a genome of a target cell upon infection of the cell by the viral particle. Such integration may be mediated by viral enzymes carried by the viral particle. In some embodiments, a viral particle as described herein further comprises an enzyme, e.g., an integrase, or a nucleic acid encoding same, such that a nucleotide of interest is integrated into a genome of a target cell upon infection of the target cell by the viral particle.

[01113] In some embodiments, a viral particle described herein is designed such that a nucleotide of interest remains episomal to a genome of a target cell upon infection of the target cell by the viral particle. In some embodiments, a viral particle described herein lacks an enzyme that mediates integration of a nucleotide of interest, e.g., an integrase, or a nucleic acid encoding same.

[01114] In some embodiments, the viral particle described herein comprises components, e.g., capsomers, glycoproteins, etc., from a virus selected from the group consisting of Human Immunodeficiency Virus (HIV), Bovine Immunodeficiency Virus (BIV), Feline Immunodeficiency Virus (FIV), Simian Immunodeficiency Virus (SIV), Equine Infectious Anemia Virus (EIAV), Murine Stem Cell Virus (MSCV), or Murine Leukemia Virus (MLV). In some embodiments, a viral particle described herein comprises an HIV capsomer, a plurality of HIV capsomers, and/or an HIV capsid, e.g., is a HIV viral particle and/or is derived from HIV.

[01115] In some embodiments, a viral particle as described herein displays a fusogen. In some embodiments, the fusogen is a protein; e.g., a viral protein (e.g., a vesiculovirus protein [e.g., vesicular stomatitis virus G glycoprotein (VSVG)], an alphavirus protein [e.g., a Sindbis virus glycoprotein], an orthomyxovirus protein [e.g., an influenza HA protein], a paramyxovirus protein [e.g., a Nipah virus F protein or a measles virus F protein]), a retrovirus protein, a lentivirus protein, or a fragment, mutant or derivative thereof. In one specific embodiment, the fusogen is heterologous to the reference wild type virus from which the particle is derived. In some embodiments, the fusogen is a mutated protein which does not bind its natural ligand.

[01116] In some embodiments, the viral particles described herein are replication deficient and only contain an incomplete genome of the virus from which they are derived. For example, in some embodiments, the lentiviral and retroviral particles do not comprise the genetic information of the gag, env, or pol genes (which may be involved in the assembly of the viral particle), which is a known minimal requirement for successful replication of a lentivirus or retrovirus. In some

embodiments, the retrovirus is a lentivirus. In these cases, the minimal set of viral proteins needed to assemble the vector particle are provided in trans by means of a packaging cell line. In one specific embodiment, for lentiviral particles derived from HIV-1, env, tat, vif, vpu and nef genes are lacking and are not provided in trans or are made inactive by the use of frame shift mutation(s).

[01117] In some embodiments, an RNA molecule which can be incorporated into the lentiviral or retroviral particles comprises the psi packaging signal and LTRs. In some embodiments, the RNA molecule incorporated into the lentiviral or retroviral particles comprises a nucleotide sequence of interest. To achieve expression of such nucleotide sequence of interest in the target cell, such sequence is can be placed under the control of a suitable promoter, for example, the CMV promoter.

[01118] In some embodiments of lentiviral and retroviral particles, RNA molecule together with the gag and pol encoded proteins, provided in trans by the packaging cell line, are then assembled into the vector particles, which then infect their target cells, reverse-transcribe the RNA molecule that may comprise a nucleotide sequence of interest under the control of a promoter, and either integrate said genetic information into the genome of the target cells or remain episomal (if one or more of the components required for integration are disrupted). If the genetic information for the gag and pol encoded proteins is not present on the transduced RNA molecule, the vector particles are replication deficient, i.e., no new generation of said vector particles will thus be generated by the transduced cell, thus ensuring safety in clinical applications.

[01119] In some embodiments, the viral particle and/or viral vector is derived from an adeno-associated virus (AAV). "AAV" is an abbreviation for adeno-associated virus and may be used to refer to the virus itself or derivatives thereof. AAVs are small, non-enveloped, single-stranded DNA viruses. Generally, a wildtype AAV genome is 4.7 kb and is characterized by two inverted terminal repeats (ITR) and two open reading frames (ORFs), *rep* and *cap.* The wildtype *rep* reading frame encodes four proteins of molecular weight 78 kD (“Rep78”), 68 kD (“Rep68”), 52 kD (“Rep52”) and 40 kD (“Rep 40”). Rep78 and Rep68 are transcribed from the p5 promoter, and Rep52 and Rep40 are transcribed from the p19 promoter. These proteins function mainly in regulating the transcription and replication of the AAV genome. The wildtype *cap* reading frame encodes three structural (capsid) viral proteins (VPs) having molecular weights of 83-85 kD (VP1), 72-73 kD (VP2) and 61-62 kD (VP3). More than 80% of total proteins in an AAV virion (capsid) comprise VP3; in mature virions, VP1, VP2 and VP3 are found at relative abundance of

approximately 1:1:10, although ratios of 1:1:8 have been reported. Padron et al. (2005) J. Virology 79:5047-58.

[01120] The genomic sequences of various serotypes of AAV, as well as the sequences of the native inverted terminal repeats (ITRs), Rep proteins, and capsid subunits are known in the art. Such sequences may be found in the literature or in public databases such as GenBank. See, e.g., GenBank Accession Numbers NC_002077 (AAV1), AF063497 (AAV1), NC001401 (AAV-2), AF043303 (AAV2), NC_001729 (AAV3), NC_001829 (AAV4), U89790 (AAV4), NC_006152 (AAV5), AF513851 (AAV7), AF513852 (AAV8), and NC_006261 (AAV8); the disclosures of which are incorporated by reference herein for teaching AAV nucleic acid and amino acid sequences. See also, e.g., Srivistava et al. (1983) J. Virology 45:555; Chiorini et al. (1998) J. Virology 71:6823; Chiorini et al. (1999) J. Virology 73: 1309; Bantel-Schaal et al. (1999) J. Virology 73:939; Xiao et al. (1999) J. Virology 73:3994; Muramatsu et al. (1996) Virology 221:208; Shade et al.,(1986) J. Virol. 58:921; Gao et al. (2002) Proc. Nat. Acad. Sci. USA 99: 11854; Moris et al. (2004) Virology 33:375-383; US Patent Publication 20170130245; international patent publications WO 00/28061, WO 99/61601, WO 98/11244; and U.S. Pat. No. 6,156,303, each of which is incorporated by reference in its entirety by reference.

[01121] "AAV" encompasses all subtypes and both naturally occurring and modified forms, except where stated otherwise. AAV includes primate AAV (e.g., AAV type 1 (AAV1), primate AAV type 2 (AAV2), primate AAV type 3 (AAV3), primate AAV3B, primate AAV type 4 (AAV4), primate AAV type 5 (AAV5), primate AAV type 6 (AAV6), primate AAV6.2, primate AAV type 7 (AAV7), primate AAV type 8 (AAV8), primate AAV type 9 (AAV9), AAV10, AAV type hu11 (AAV hu11), AAV11, AAV12, AAV13, AAVDJ, Anc80L65, AAV2G9, AAVLK03, AAV type rh32.33 (AAVrh.32.33), AAV retro (AAV retro), AAV PHP.B, AAV PHP.eB, AAV PHP.S, AAVrh.64R1, AAVhu.37, AAVrh.8, AAV2/8, etc.; non-primate animal AAV (e.g., avian AAV (AAAV)) and other non-primate animal AAV such as mammalian AAV (e.g., bat AAV, sea lion AAV, bovine AAV, canine AAV, equine AAV, caprine AAV, and ovine AAV etc.), squamate AAV (e.g., snake AAV, bearded dragon AAV), etc., "Primate AAV" refers to AAV generally isolated from primates. Similarly, "non-primate animal AAV" refers to AAV isolated from non-primate animals.

[01122] As used herein, "of a [specified] AAV" in relation to a gene (e.g., *rep*, *cap*, etc.), capsid protein (e.g., a VP1 capsid protein, a VP2 capsid protein, a VP3 capsid protein, etc.), region of a capsid protein of a specified AAV (e.g., PLA_2 region, VP1-u region, VP1/VP2 common region, VP3 region), nucleotide sequence (e.g., ITR sequence), e.g., a *cap* gene or capsid protein of AAV etc., encompasses, in addition to the gene or the polypeptide respectively comprising a nucleic acid sequence or amino acid sequence set forth herein for the specified AAV, also

variants of the gene or polypeptide, including variants comprising the least number of nucleotides or amino acids required to retain one or more biological functions. As used herein, a variant gene or a variant polypeptide comprises a nucleic acid sequence or amino acid sequence that differs from the nucleic acid sequence or amino acid sequence set forth herein for the gene or polypeptide of a specified AAV, wherein the difference(s) does not generally alter at least one biological function of the gene or polypeptide, and/or the phylogenetic characterization of the gene or polypeptide, e.g., where the difference(s) may be due to degeneracy of the genetic code, isolate variations, length of the sequence, etc. For example, *rep* gene and the *cap* gene as used here may encompass *rep* and *cap* genes that differ from the wildtype gene in that the genes may encode one or more Rep proteins and Cap proteins, respectively. In some embodiments, a Rep gene encodes at least Rep78 and/or Rep68. In some embodiments, *cap* gene includes those may differ from the wildtype in that one or more alternative start codons or sequences between one or more alternative start codons are removed such that the *cap* gene encodes only a single Cap protein, e.g., wherein the VP2 and/or VP3 start codons are removed or substituted such that the *cap* gene encodes a functional VP1 capsid protein but not a VP2 capsid protein or a VP3 capsid protein. Accordingly, as used herein, a *rep* gene encompasses any sequence that encodes a functional Rep protein. A *cap* gene encompasses any sequence that encodes at least one functional *cap* gene.

[01123] It is well-known that the wildtype *cap* gene expresses all three VP1, VP2, and VP3 capsid proteins from a single open reading frame of the *cap* gene under control of the p40 promoter found in the *rep* ORF. The term "capsid protein," "Cap protein," and the like, include a protein that is part of the capsid of the virus. For adeno-associated viruses, the capsid proteins are generally referred to as VP1, VP2 and/or VP3, and may be encoded by the single *cap* gene. For AAV, the three AAV capsid proteins are produced in nature an overlapping fashion from the *cap* ORF alternative translational start codon usage, although all three proteins use a common stop codon. The ORF of a wildtype *cap* gene encodes from 5' to 3' three alternative start codons: "the VP1 start codon," "the VP2 start codon," and "the VP3 start codon"; and one "common stop codon". The largest viral protein, VP1, is generally encoded from the VP1 start codon to the "common stop codon." VP2 is generally encoded from the VP2 start codon to the common stop codon. VP3 is generally encoded from the VP3 start codon to the common stop codon. Accordingly, VP1 comprises at its N-terminus sequence that it does not share with the VP2 or VP3, referred to as the VP1-unique region (VP1-u). The VP1-u region is generally encoded by the sequence of a wildtype *cap* gene starting from the VP1 start codon to the "VP2 start codon." VP1-u comprises a phospholipase A2 domain (PLA_2), which may be important for

infection, as well as nuclear localization signals which may aid the virus in targeting to the nucleus for uncoating and genome release. The VP1, VP2, and VP3 capsid proteins share the same C-terminal sequence that makes up the entirety of VP3, which may also be referred to herein as the VP3 region. The VP3 region is encoded from the VP3 start codon to the common stop codon. VP2 has an additional ~ 60 amino acids that it shares with the VP1. This region is called the VP1/VP2 common region.

[01124] In some embodiments, one or more of the Cap proteins of the invention may be encoded by one or more *cap* genes having one or more ORFs. In some embodiments, the VP proteins of the invention may be expressed from more than one ORF comprising nucleotide sequence encoding any combination of VP1, VP2, and/or VP3 by use of separate nucleotide sequences operably linked to at least one expression control sequence for expression in packaging cell, each producing one or more of VP1, VP2, and/or VP3 capsid proteins of the invention. In some embodiments, a VP capsid protein of the invention may be expressed individually from an ORF comprising nucleotide sequence encoding any one of VP1, VP2, or VP3 by use of separate nucleotide sequences operably linked to one expression control sequence for expression in a viral replication cell, each producing only one of VP1, VP2, or VP3 capsid protein. In another embodiment, VP proteins may be expressed from one ORF comprising nucleotide sequences encoding VP1, VP2, and VP3 capsid proteins operably linked to at least one expression control sequence for expression in a viral replication cell, each producing VP1, VP2, and VP3 capsid protein. Accordingly, although amino acid positions may be provided in relation to the VP1 capsid protein of the referenced AAV, a skilled artisan would be able to respectively and readily determine the position of that same amino acid within the VP2 and/or VP3 capsid protein of the AAV, and the corresponding position of amino acids among different AAV.

[01125] The phrase “Inverted terminal repeat” or “ITR” includes symmetrical nucleic acid sequences in the genome of adeno-associated viruses required for efficient replication. ITR sequences are located at each end of the AAV DNA genome. The ITRs serve as the origins of replication for viral DNA synthesis and are essential cis components for generating AAV particles, e.g., packaging into AAV particles.

[01126] AAV ITR comprise recognition sites for replication proteins Rep78 or Rep68. A "D" region of the ITR comprises the DNA nick site where DNA replication initiates and provides directionality to the nucleic acid replication step. An AAV replicating in a mammalian cell typically comprises two ITR sequences.

[01127] A single ITR may be engineered with Rep binding sites on both strands of the "A" regions and two symmetrical D regions on each side of the ITR palindrome. Such an engineered construct on a double-stranded circular DNA template allows Rep78 or Rep68 initiated nucleic acid replication that proceeds in both directions. A single ITR is sufficient for AAV replication of a circular particle. In methods of producing an AAV viral particle of the invention, the *rep* encoding sequence encodes a Rep protein or Rep protein equivalent that is capable of binding an ITR comprised on the transfer plasmid.

[01128] The Cap proteins of the invention, when expressed with appropriate Rep proteins by a packaging cell, may encapsidate a transfer plasmid comprising a nucleotide of interest and an even number of two or more ITR sequences. In some embodiments, a transfer plasmid comprises one ITR sequence. In some embodiments, a transfer plasmid comprises two ITR sequences.

[01129] Either Rep78 and/or Rep68 bind to unique and known sites on the sequence of the ITR hairpin, and act to break and unwind the hairpin structures on the end of an AAV genome, thereby providing access to replication machinery of the viral replication cell. As is well-known, Rep proteins may be expressed from more than one ORF comprising nucleotide sequence encoding any combination of Rep78, Rep68, Rep 52 and/or Rep40 by use of separate nucleotide sequences operably linked to at least one expression control sequence for expression in a viral replication cell, each producing one or more of Rep78, Rep68, Rep 52 and/or Rep40 Rep proteins. Alternatively, Rep proteins may be expressed individually from an ORF comprising a nucleotide sequence encoding any one of Rep78, Rep68, Rep 52, or Rep40 by use of separate nucleotide sequences operably linked to one expression control sequence for expression in a packaging cell, each producing only one Rep78, Rep68, Rep 52, or Rep40 Rep protein. In another embodiment, Rep proteins may be expressed from one ORF comprising nucleotide sequences encoding Rep78 and Rep52 Rep proteins operably linked to at least one expression control sequence for expression in a viral replication cell each producing Rep78 and Rep52 Rep protein.

[01130] In a method of producing an AAV virion, e.g., viral particle, of the invention, a *rep* encoding sequence and a *cap* gene of the invention may be provided a single packaging plasmid. However, a skilled artisan will recognize that such proviso is not necessary. Such viral particles may or may not include a genome.

[01131] A "chimeric AAV capsid protein" includes an AAV capsid protein that comprises amino acid sequences, e.g., portions, from two or more different AAV and that is capable of forming and/or forms an AAV viral capsid/viral particle. A chimeric AAV capsid protein is encoded by a

chimeric AAV capsid gene, e.g., a chimeric nucleotide comprising a plurality, e.g., at least two, nucleic acid sequences, each of which plurality is identical to a portion of a capsid gene encoding a capsid protein of distinct AAV, and which plurality together encodes a functional chimeric AAV capsid protein. Association of a chimeric capsid protein to a specific AAV indicates that the capsid protein comprises one or more portions from a capsid protein of that AAV and one or more portions from a capsid protein of a different AAV. For example, a chimeric AAV2 capsid protein includes a capsid protein comprising one or more portions of a VP1, VP2, and/or VP3 capsid protein of AAV2 and one or more portions of a VP1, VP2, and/or VP3 capsid protein of a different AAV.

[01132] In some embodiments, a Cap protein, e.g., a VP1 capsid protein as described herein, a VP2 capsid protein as described herein, and/or a VP3 capsid protein as described herein, is modified to comprise e.g., a first member of a protein:protein binding pair, a detectable label, point mutation, etc.

[01133] Chimerism is a type of modification as described herein. Generally, modification of gene or a polypeptide of a specified AAV, or variants thereof, results in nucleic acid sequence or an amino acid sequence that differs from the nucleic acid sequence or amino acid sequence set forth herein for the specified AAV, wherein the modification alters, confers, or removes one or more biological functions, but does not change the phylogenetic characterization of, the gene or polypeptide. A modification may include an insertion of, e.g., a first member of a protein:protein binding pair and a point mutation, e.g., such that the natural tropism of the capsid protein is reduced or abolished and/or such that the capsid protein comprises a detectable label. Modifications can include those that either do not alter or decrease the likelihood that the modified capsid will be recognized by pre-existing antibodies found in the general population, e.g., antibodies produced during the course of previous infection(s) with an AAV, e.g., infection(s) with serotypes such as AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAV10, AAV11, AAV12, AAV13, AAVDJ, Anc80L65, AAV2G9, AAV-LK03, virions based on such serotypes, virions from currently used AAV gene therapy modalities, or a combination thereof. Other modifications as described herein include modification of a capsid protein such that it comprises a first member of a protein:protein binding pair, a detectable label, etc., which modifications generally result from modifications at the genetic level, e.g., via modification of a *cap* gene.

[01134] In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein is a mosaic capsid, e.g., which comprises at least two sets of VP1, VP2, and/or VP3 proteins, each set of which is encoded by a different *cap* gene. A mosaic capsid

herein generally refers to a mosaic of a first viral capsid protein modified to comprise a first member of a protein:protein binding pair and a second corresponding viral capsid protein lacking the first member of a protein:protein binding pair. In relation to a mosaic capsid, the second viral capsid protein lacking the first member of a protein:protein binding pair may be referred to as a reference capsid protein encoded by a reference *cap* gene. In some mosaic capsid embodiments, preferably when the VP1, VP2, and/or VP3 capsid proteins modified with a first member of protein:protein pair is not a chimeric capsid protein, a VP1, VP2, and/or VP3 reference capsid protein may comprise an amino acid sequence identical to that of the viral VP1, VP2, and/or VP3 capsid protein modified with a first member of a protein:protein binding pair, except that the reference capsid protein lacks the first member of a protein:protein binding pair. In some mosaic capsid embodiments, a VP1, VP2, and/or VP3 reference capsid protein corresponds to the viral VP1, VP2, and/or VP3 capsid protein modified with a first member of a protein:protein binding pair, except that the reference capsid protein lacks the first member of a protein:protein binding pair. In some embodiments, a VP1 reference capsid protein corresponds to the viral VP1 capsid protein modified with a first member of a protein:protein binding pair, except that the reference capsid protein lacks the first member of a protein:protein binding pair. In some embodiments, a VP2 reference capsid protein corresponds to the viral VP2 capsid protein modified with a first member of a protein:protein binding pair, except that the reference capsid protein lacks the first member of a protein:protein binding pair. In some embodiments, a VP3 reference capsid protein corresponds to the viral VP3 capsid protein modified with a first member of a protein:protein binding pair, except that the reference capsid protein lacks the first member of a protein:protein binding pair. In some mosaic capsid embodiments comprising a chimeric VP1, VP2, and/or VP3 capsid protein further modified to comprise a first member of a protein:protein binding pair, a reference protein may be a corresponding capsid protein from which portions thereof form part of the chimeric capsid protein. As a non-limiting example, in some embodiments, a mosaic capsid comprising a chimeric AAV2/AAAV VP1 capsid protein modified to comprise a first member of a protein:protein binding pair may further comprise as a reference capsid protein: an AAV2 VP1 capsid protein lacking the first member, an AAAV VP1 capsid protein lacking the first member, a chimeric AAV2/AAAV VP1 capsid protein lacking the first member. Similarly, in some embodiments, a mosaic capsid comprising a chimeric AAV2/AAAV VP2 capsid protein modified to comprise a first member of a protein:protein binding pair may further comprise as a reference capsid protein: an AAV2 VP2 capsid protein lacking the first member, an AAAV VP1 capsid protein lacking the first member, a chimeric AAV2/AAAV VP2 capsid protein lacking the first member. In some embodiments, a mosaic capsid comprising

a chimeric AAV2/AAAV VP3 capsid protein modified to comprise a first member of a protein:protein binding pair may further comprise as a reference capsid protein: an AAV2 VP2 capsid protein lacking the first member, an AAAV VP1 capsid protein lacking the first member, a chimeric AAV2/AAAV VP3 capsid protein lacking the first member. In some mosaic capsid embodiments, a reference capsid protein may be any capsid protein so long as it that lacks the first member of the protein:protein binding pair and is able to form a capsid with the first capsid protein modified with the first member of a protein:protein binding pair.

[01135] Generally mosaic particles may be generated by transfecting mixtures of the modified and reference *Cap* genes into production cells at the indicated ratios. The protein subunit ratios, e.g., modified VP protein:unmodified VP protein ratios, in the particle may, but do not necessarily, stoichiometrically reflect the ratios of the at least two species of the *cap* gene encoding the first capsid protein modified with a first member of a protein:protein binding pair and the one or more reference *cap* genes, e.g., modified *cap* gene:reference *cap* gene(s) transfected into packaging cells. In some embodiments, the protein subunit ratios in the particle do not stoichiometrically reflect the modified *cap* gene:reference *cap* gene(s) ratio transfected into packaging cells.

[01136] In some mosaic viral particle embodiments, the protein subunit ratio ranges from about 1:59 to about 59:1. In some mosaic viral particle embodiments, the protein subunit is at least about 1:1 (e.g., the mosaic viral particle comprises about 30 modified capsid proteins and about 30 reference capsid protein). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:2 (e.g., the mosaic viral particle comprises about 20 modified capsid proteins and about 40 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 3:5. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:3 (e.g., the mosaic viral particle comprises about 15 modified capsid proteins and about 45 reference capsid proteins) . In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:4 (e.g., the mosaic viral particle comprises about 12 modified capsid proteins and 48 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:5 (e.g., the mosaic viral particle comprises 10 modified capsid proteins and 50 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:6. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:7. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:8. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:9 (e.g., the mosaic viral particle comprises about 6 modified capsid proteins and about 54 reference capsid

proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:10. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:11 (e.g., the mosaic viral particle comprises about 5 modified capsid proteins and about 55 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:12. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:13. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:14 (e.g., the mosaic viral particle comprises about 4 modified capsid proteins and about 56 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:15. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:19 (e.g., the mosaic viral particle comprises about 3 modified capsid proteins and about 57 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:29 (e.g., the mosaic viral particle comprises about 2 modified capsid proteins and about 58 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 1:59. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 2:1 (e.g., the mosaic viral particle comprises about 40 modified capsid proteins and about 20 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 5:3. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 3:1 (e.g., the mosaic viral particle comprises about 45 modified capsid proteins and about 15 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 4:1 (e.g., the mosaic viral particle comprises about 48 modified capsid proteins and 12 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 5:1 (e.g., the mosaic viral particle comprises 50 modified capsid proteins and 10 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 6:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 7:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 8:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 9:1 (e.g., the mosaic viral particle comprises about 54 modified capsid proteins and about 6 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 10:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 11:1 (e.g., the mosaic viral particle comprises about 55 modified capsid proteins and about 5 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 12:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 13:1. In some mosaic viral particle embodiments, the

protein subunit ratio is at least about 14:1 (e.g., the mosaic viral particle comprises about 56 modified capsid proteins and about 4 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 15:1. In some mosaic viral particle embodiments, the protein subunit ratio is at least about 19:1 (e.g., the mosaic viral particle comprises about 57 modified capsid proteins and about 3 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 29:1 (e.g., the mosaic viral particle comprises about 58 modified capsid proteins and about 2 reference capsid proteins). In some mosaic viral particle embodiments, the protein subunit ratio is at least about 59:1.

[01137] In some non-mosaic viral particle embodiments, the protein subunit ratio may be 1:0 wherein each capsid protein of the non-mosaic viral particle is modified with a first member of a protein:protein binding pair. In some non-mosaic viral particle embodiments, the protein subunit ratio may be 0:1 wherein each capsid protein of the non-mosaic viral particle is not modified with a first member of a protein:protein binding pair.

[01138] In some embodiments, a capsid protein of the invention is modified to comprise a detectable label. Many detectable labels are known in the art. (See, e.g.: Nilsson et al. (1997) "Affinity fusion strategies for detection, purification, and immobilization of modified proteins" Protein Expression and Purification 11: 1-16, Terpe et al. (2003) "Overview of tag protein fusions: From molecular and biochemical fundamentals to commercial systems" Applied Microbiology and Biotechnology 60:523-533, and references therein). Detectable labels include, but are not limited to, a polyhistidine detectable labels (e.g., a His-6 (SEQ ID NO: 1110), His-8 (SEQ ID NO: 1111), or His-10 (SEQ ID NO: 1112)) that binds immobilized divalent cations (e.g., Ni^{2+}), a biotin moiety (e.g., on an *in vivo* biotinylated polypeptide sequence) that binds immobilized avidin, a GST (glutathione S-transferase) sequence that binds immobilized glutathione, an S tag that binds immobilized S protein, an antigen that binds an immobilized antibody or domain or fragment thereof (including, e.g., T7, myc, FLAG, and B tags that bind corresponding antibodies), a FLASH Tag (a high detectable label that couples to specific arsenic based moieties), a receptor or receptor domain that binds an immobilized ligand (or vice versa), protein A or a derivative thereof (e.g., Z) that binds immobilized IgG, maltose-binding protein (MBP) that binds immobilized amylose, an albumin-binding protein that binds immobilized albumin, a chitin binding domain that binds immobilized chitin, a calmodulin binding peptide that binds immobilized calmodulin, and a cellulose binding domain that binds immobilized cellulose. Another exemplary detectable label is a SNAP-tag, such as that which is commercially available from Covalys. In some embodiments, a detectable label disclosed herein

comprises a detectable label recognized only by an antibody paratope. In some embodiments, a detectable label disclosed herein comprises a detectable label recognized by an antibody paratope and other specific binding pairs.

[01139] In some embodiments, the detectable label forms a binding pair with an immunoglobulin constant domain. In some embodiments, the detectable label and/or detectable label does form a binding pair with a metal ion, e.g., Ni^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Fe^{3+}, etc. In some embodiments, the detectable label is selected from the group consisting of Streptavidin, Strep II, HA, L14, 4C-RGD, LH, and Protein A.

[01140] In some embodiments, the detectable label is selected from the group consisting of FLAG, HA and c-myc.

[01141] In some embodiments, a detectable label is a B cell epitope, e.g., which is between about 1 amino acid and about 35 amino acids in length, and forms a binding pair with an antibody paratope, e.g., an immunoglobulin variable domain. In some embodiments, the detectable label comprises a B1 epitope. In some embodiments, a capsid protein is modified to comprise a B1 epitope in the VP3 region.

[01142] In some embodiments, a capsid protein of the invention comprises at least a first member of a peptide:peptide binding pair.

[01143] In some embodiments, a capsid protein of the invention comprises a first member of a protein:protein binding pair comprising a detectable label, which may also be used for the detection and/or isolation of the Cap protein and/or as a first member of a protein:protein binding pair. In some embodiments, a detectable label acts as a first member of a protein:protein binding pair for the binding of a targeting ligand comprising a multispecific binding protein that may bind both the detectable label and a target expressed by a cell of interest. In some embodiments, a Cap protein of the invention comprises a first member of a protein:protein binding pair comprising c-myc. Use of a detectable label as a first member of a protein:protein binding pair is described in, e.g., WO2019006043, incorporated herein in its entirety by reference.

[01144] In some embodiments, a capsid protein comprises a first member of a protein:protein binding pair, wherein the protein:protein binding pair forms a covalent isopeptide bond. In some embodiments, the first member of a peptide:peptide binding pair is covalently bound via an isopeptide bond to a cognate second member of the peptide:peptide binding pair, and optionally wherein the cognate second member of the peptide:peptide binding pair is fused with a targeting ligand, which targeting ligand binds a target expressed by a cell of interest. In some embodiments, the protein:protein binding pair may be selected from the group consisting of

SpyTag:SpyCatcher, SpyTag002:SpyCatcher002, SpyTag:KTag, Isopeptag:pilinC, and SnoopTag:SnoopCatcher. In some embodiments, the first member is SpyTag (or a biologically active portion thereof) and the protein (second cognate member) is SpyCatcher (or a biologically active portion thereof). In some embodiments, the first member is SpyTag (or a biologically active portion thereof) and the protein (second cognate member) is KTag (or a biologically active portion thereof). In some embodiments, the first member is KTag (or a biologically active portion thereof) and the protein (second cognate member) is SpyTag (or a biologically active portion thereof). In some embodiments, the first member is SnoopTag (or a biologically active portion thereof) and the protein (second cognate member) is SnoopCatcher (or a biologically active portion thereof). In some embodiments, the first member is Isopeptag (or a biologically active portion thereof) and the protein (second cognate member) is Pilin-C (or a biologically active portion thereof). In some embodiments, the first member is SpyTag002 (or a biologically active portion thereof) and the protein (second cognate member) is SpyCatcher002 (or a biologically active portion thereof). In some embodiments, a Cap protein of the invention comprises a SpyTag. Use of a first member of a protein:protein binding pair is described in WO2019006046, incorporated herein in its entirety.

[01145] In some embodiments, a first member of a protein:protein binding pair and/or detectable label is operably linked to (translated in frame with, chemically attached to, and/or displayed by) a Cap protein of the invention via a first or second linker, e.g., an amino acid spacer that is at least one amino acid in length. In some embodiments, the first member of a protein:protein binding pair is flanked by a first and/or second linker, e.g., a first and/or second amino acid spacer, each of which spacer is at least one amino acid in length.

[01146] In some embodiments, the first and/or second linkers are not identical. In some embodiments, the first and/or second linker is each independently one or two amino acids in length. In some embodiments, the first and/or second linker is each independently one, two or three amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, or four amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, or five amino acids in length. In some embodiments, the first and/or second linker are each independently one, two, three, four, or five amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, or six amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, six, or seven amino acids in length. In some embodiments, the first and/or second linker is each independently one, two, three, four, five, six, seven, or eight amino acids in length. In some embodiments, the first

and/or second linker is each independently one, two, three, four, five, six, seven, eight or nine amino acids in length. In some embodiments, the first and or second linker is each independently one, two, three, four, five, six, seven, eight, nine, or ten amino acids in length. In some embodiments, the first and or second linker is each independently one, two, three, four, five, six, seven, eight, nine, ten, or more amino acids in length.

[01147] In some embodiments, the first and second linkers are identical in sequence and/or in length and are each one amino acid in length. In some embodiments, the first and second linkers are identical in length, and are each one amino acid in length. In some embodiments, the first and second linkers are identical in length, and are each two amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each three amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each four amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each five amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each six amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each seven amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each eight amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each nine amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each ten amino acids in length. In some embodiments, the first and second linkers are identical in length, and are each more than ten amino acids in length.

[01148] Generally, a first member of a protein:protein binding pair amino acid sequence as described herein, e.g., comprising a first member of a specific binding pair by itself or in combination with one or more linkers, is between about 5 amino acids and about 50 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is at least 5 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 6 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 7 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 8 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 9 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 10 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 11 amino acids in length. In some embodiments, the first member of a

protein:protein binding pair amino acid sequence is 12 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 13 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 14 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 15 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 16 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 17 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 18 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 19 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 20 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 21 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 22 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 23 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 24 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 25 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 26 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 27 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 28 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 29 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 30 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 31 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 32 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 33 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 34 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 35 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 36 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 37

amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 38 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 39 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 40 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 41 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 42 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 43 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 44 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 45 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 46 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 47 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 48 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 49 amino acids in length. In some embodiments, the first member of a protein:protein binding pair amino acid sequence is 50 amino acids in length.

[01149] Due to the high conservation of at least large stretches and the large member of closely related family members, the corresponding insertion sites for AAV other than the enumerated AAV can be identified by performing an amino acid alignment or by comparison of the capsid structures. *See, e.g.*, *Rutledge et al*. (1998) *J. Virol.* 72:309-19; Mietzsch et al. (2019) *Viruses* 11, 362, 1-34, and U.S. Patent No. 9,624,274 for exemplary alignments of different AAV capsid proteins, each of which is incorporated herein by reference in its entirety. For example, Mietzsch et al. (2019) provide an overlay of ribbons from different dependoparvovirus at Figure 7, depicting the variable regions VR I to VR IX. Using such structural analysis as described therein, and sequence analysis, a skilled artisan may determine which amino acids within the variable region correspond to amino acid sequence of AAV that can accommodate the insertion of a first member of a protein:protein binding pair and/or detectable label.

[01150] Accordingly, in some embodiments, the first member of a protein:protein binding pair and/or detectable label is inserted in a VP1 capsid protein of a non-primate animal AAV after an amino acid position corresponding with an amino acid position selected from the group consisting of G453 of AAV2 capsid protein VP1, N587 of AAV2 capsid protein VP1, G453 of AAV9 capsid protein VP1, and A589 of AAV9 capsid protein VP1. In some embodiments, the

first member of a protein:protein binding pair and/or detectable label is inserted in a VP1 capsid protein of a non-primate animal AAV between amino acids that correspond with N587 and R588 of an AAV2 VP1 capsid. Additional suitable insertion sites of a non-primate animal VP1 capsid protein include those corresponding to I-1, I-34, I-138, I-139, I-161, I261, I-266, I-381, I-453, I-447, I-448, I-459, I-471, I-520, I-534, I-570, I-573, I-584, I-587, I-588, I591, I-657, I-664, I-713 and I-716 of the VP1 capsid protein of AAV2 (Wu et al. (2000) *J. Virol.* 74:8635-8647). In some embodiments, an insertion site of a non-primate animal VP1 capsid protein corresponds to I-453. A modified virus capsid protein as described herein may be a non-primate animal capsid protein comprising a first member of a protein:protein binding pair and/or detectable label inserted into a position corresponding with a position of an AAV2 capsid protein selected from the group consisting of I-1, I-34, I-138, I-139, I-161, I261, I-266, I-381, I-447, I-448, I-453, I-459, I-471, I-520, I-534, I-570, I-573, I-584, I-587, I-588, I591, I-657, I-664, I-713, I-716, and a combination thereof. In some embodiments, an insertion site of a non-primate animal VP1 capsid protein corresponds to I-453. Additional suitable insertion sites of a non-primate animal AAV that include those corresponding to I-587 of AAV1, I-589 of AAV1, I-585 of AAV3, I-585 of AAV4, and I-585 of AAV5. In some embodiments, a modified virus capsid protein as described herein may be a non-primate animal capsid protein comprising a first member of a protein:protein binding pair and/or detectable label inserted into a position corresponding with a position selected from the group consisting of I-587 (AAV1), I-589 (AAV1), I-585 (AAV3), I-585 (AAV4), I-585 (AAV5), and a combination thereof.

[01151] In some embodiments, the first member of a protein:protein binding pair and/or detectable label is inserted in a VP1 capsid protein of a non-primate animal AAV after an amino acid position corresponding with an amino acid position selected from the group consisting of I444 of an avian AAV capsid protein VP1, I580 of an avian AAV capsid protein VP1, I573 of a bearded dragon AAV capsid protein VP1, I436 of a bearded dragon AAV capsid protein VP1, I429 of a sea lion AAV capsid protein VP1, I430 of a sea lion AAV capsid protein VP1, I431 of a sea lion AAV capsid protein VP1, I432 of a sea lion AAV capsid protein VP1, I433 of a sea lion AAV capsid protein VP1, I434 of a sea lion AAV capsid protein VP1, I436 of a sea lion AAV capsid protein VP1, I437 of a sea lion AAV capsid protein VP1, and I565 of a sea lion AAV capsid protein VP1.

[01152] The nomenclature I-###, I# or the like herein refers to the insertion site (I) with ### naming the amino acid number relative to the VP1 protein of an AAV capsid protein, however such the insertion may be located directly N- or C-terminal, preferably C-terminal of one amino acid in the sequence of 5 amino acids N- or C-terminal of the given amino acid, preferably 3,

more preferably 2, especially 1 amino acid(s) N- or C-terminal of the given amino acid. Additionally, the positions referred to herein are relative to the VP1 protein encoded by an AAV capsid gene, and corresponding positions (and point mutations thereof) may be easily identified for the VP2 and VP3 capsid proteins encoding by the capsid gene by performing a sequence alignment of the VP1, VP2 and VP3 proteins encoded by the appropriate AAV capsid gene.

[01153] Accordingly, an insertion into the corresponding position of the coding nucleic acid of one of these sites of the cap gene leads to an insertion into VP1, VP2 and/or VP3, as the capsid proteins are encoded by overlapping reading frames of the same gene with staggered start codons. Therefore, for AAV2, for example, according to this nomenclature insertions between amino acids 1 and 138 are only inserted into VP1, insertions between 138 and 203 are inserted into VP1 and VP2, and insertions between 203 and the C-terminus are inserted into VP1, VP2 and VP3, which is of course also the case for the insertion site I-587. Therefore, the present invention encompasses structural genes of AAV with corresponding insertions in the VP1, VP2 and/or VP3 proteins.

[01154] Also provided herein are nucleic acids that encode a VP3 capsid protein of the invention. AAV capsid proteins may be, but are not necessarily, encoded by overlapping reading frames of the same gene with staggered start codons. In some embodiments, a nucleic acid that encodes a VP3 capsid protein of the invention does not also encode a VP2 capsid protein or VP1 capsid protein of the invention. In some embodiments, a nucleic acid that encodes a VP3 capsid protein of the invention may also encode a VP2 capsid protein of the invention but does not also encode a VP1 capsid of the invention. In some embodiments, a nucleic acid that encodes a VP3 capsid protein of the invention may also encode a VP2 capsid protein of the invention and a VP1 capsid of the invention.

[01155] In some embodiments, a viral capsid comprising the modified viral capsid protein comprising the first and second members of a protein:protein binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.) is able to infect a specific cell, e.g., has an enhanced capacity to target and bind a specific cell compared to that of a control viral capsid that is identical to the modified viral capsid protein except that it lacks either or both the first and second members of a protein:protein binding pair, e.g., comprises a control capsid protein. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a detectable transduction efficiency compared to the undetectable transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as

described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 10% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 20% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 30% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 40% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 50% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 60% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 70% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 75% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 80% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 85% greater than the transduction efficiency of a control viral capsid. In some embodiments, a

viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 90% greater than the transduction efficiency of a control capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 95% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 99% greater than the transduction efficiency of a control viral capsid.

[01156] In some embodiments, a viral capsid comprising the modified viral capsid protein comprising the first and second members of a protein:protein binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.) is able to infect a specific cell, e.g., has an enhanced capacity to target and bind a specific cell compared to that of a control viral capsid that is identical to the modified viral capsid protein except that it lacks either or both the first and second members of a protein:protein binding pair, e.g., comprises a control capsid protein. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a detectable transduction efficiency compared to the undetectable transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 10% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 20% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 30% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 40% greater than the transduction efficiency of a control viral capsid. In some embodiments, a

viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 50% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 60% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 70% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 75% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 80% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 85% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 90% greater than the transduction efficiency of a control capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 95% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is 99% greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 1.5-fold greater than the transduction

efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 2-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 3-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 4-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 5-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 6-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 7-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 8-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 9-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 10-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second

members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 20-fold greater than the transduction efficiency of a control capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to an appropriate the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 30-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 40-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 50-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 60-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 70-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 80-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 90-fold greater than the transduction efficiency of a control viral capsid. In some embodiments, a viral capsid comprising a modified viral capsid protein as described herein bound to the first and second members of a protein:protein binding pair linked to a targeting ligand exhibits a transduction efficiency that is at least 100-fold greater than the transduction efficiency of a control viral capsid In some embodiments, a viral particle of the invention comprising a viral capsid protein comprising an amino acid sequence of a capsid protein of a non-primate animal AAV, a remote AAV, or a combination thereof, and optionally comprising a first and second members of a protein:protein binding pair (e.g., wherein the second member is operably linked to a targeting ligand,

comprises a multispecific binding protein, etc.) is better able to evade neutralization by pre-existing antibodies in serum isolated from a human subject compared to an appropriate control viral particle (e.g., comprising a viral capsid of an AAV serotype from which a portion is included in the viral capsid of the invention, e.g., as part of the viral capsid protein comprising an amino acid sequence of a capsid protein of a non-primate animal AAV, a remote AAV, or a combination thereof), which also optionally comprises a first and second members of a protein:protein binding pair (e.g., wherein the second member is operably linked to a targeting ligand, comprises a multispecific binding protein, etc.). In some embodiments, a viral particle of the invention comprising a viral capsid protein comprising an amino acid sequence of a capsid protein of a non-primate animal AAV, a remote AAV, or a combination thereof requires at least 2-fold more total IVIG or IgG for neutralization (e.g., 50% or more infection inhibition) compared to an appropriate control viral particle, e.g., (e.g., a viral particle of the invention has an IC_{50} value that is at least 2-fold that of a control virus particle).

[01157] In some embodiments of the invention comprising a detectable label, a targeting ligand comprises a multispecific binding molecule comprising (i) an antibody paratope that specifically binds the detectable label and (ii) a second binding domain that specifically binds a receptor, which may be conjugated to the surface of a bead (e.g., for purification) or expressed by a target cell. Accordingly, a multispecific binding molecule comprising (i) an antibody paratope that specifically binds the detectable label and (ii) a second binding domain that specifically binds a receptor targets the viral particle. Such "targeting" or "directing" may include a scenario in which the wildtype viral particle targets several cells within a tissue and/or several organs within an organism, which broad targeting of the tissue or organs is reduced to abolished by insertion of the detectable label, and which retargeting to more specific cells in the tissue or more specific organ in the organism is achieved with the multispecific binding molecule. Such retargeting or redirecting may also include a scenario in which the wildtype viral particle targets a tissue, which targeting of the tissue is reduced to abolished by insertion of the detectable label, and which retargeting to a completely different tissue is achieved with the multispecific binding molecule. An antibody paratope as described herein generally comprises at a minimum a complementarity determining region (CDR) that specifically recognizes the detectable label, e.g., a CDR3 region of a heavy and/or light chain variable domain. In some embodiments, a multispecific binding molecule comprises an antibody (or portion thereof) that comprises the antibody paratope that specifically binds the detectable label. For example, a multispecific binding molecule may comprise a single domain heavy chain variable region or a single domain light chain variable region, wherein the single domain heavy chain variable region or single

domain light chain variable region comprises an antibody paratope that specifically binds the detectable label. In some embodiments, a multispecific binding molecule may comprise an Fv region, e.g., a multispecific binding molecule may comprise an scFv, that comprises an antibody paratope that specifically binds the detectable label. In some embodiments, a multispecific binding molecule as described herein comprises an antibody paratope that specifically binds c-myc.

[01158] One embodiment of the present invention comprises a multimeric structure comprising a modified viral capsid protein of the present invention. A multimeric structure comprises at least 5, preferably at least 10, more preferably at least 30, most preferably at least 60 modified viral capsid proteins comprising a first member of a specific binding pair as described herein. They can form regular viral capsids (empty viral particles) or viral particles (capsids encapsidating a nucleotide of interest). The formation of viral particles comprising a viral genome is a highly preferred feature for use of the modified viral capsids described herein.

[01159] A further embodiment of the present invention is the use of at least one modified viral capsid protein and/or a nucleic acid encoding same, preferably at least one multimeric structure (e.g., viral particle) for the manufacture of and use in transfer of a nucleotide of interest to a target cell.

[01160] A further embodiment of the modified viral capsids described herein is their use for delivering a nucleotide of interest, e.g., a reporter gene and/or a therapeutic gene, to a target cell. Generally, packaging of a nucleotide of interest comprises replacing an AAV genome between AAV ITR sequences with a gene of interest to create a transfer plasmid, which is then encapsulated in an AAV capsid according to well-known methods Thus, a modified viral capsid as described herein may encapsulate a transfer plasmid and/or a nucleotide of interest, which may generally comprise 5' and 3' inverted terminal repeat (ITR) sequences flanking a gene of interest, e.g., reporter gene(s) or therapeutic gene(s), or a portion of the gene of interest (which may be under the control of a viral or non-viral promoter). According to well-known methods of packaging AAV viral particles, the modified viral capsids, the 5' ITR, and the 3' ITR need not be of the same AAV serotype. In one embodiment, a transfer plasmid and/or nucleotide of interest comprises from 5' to 3': a 5' ITR, a promoter, a gene (e.g., a reporter and/or therapeutic gene) and a 3'ITR.

[01161] A consideration for AAV transfer plasmid design is that a wildtype AAV genome is ~4.7kb. Thus, included herein are the well-known strategies that provide for packaging nucleotides of interest that exceed the packaging capacity of an individual AAV. Such strategies include, but are not limited to, dual-vector strategies that exploit ITR-mediated recombination to

express genes of interest that are larger than a wildtype AAV genome by way of transcript splicing across intermolecularly recombined ITRs from two complementary vector genomes, vector recombination by homology, RNA trans-splicing, and/or protein "trans-splicing" via split intein designs. See, e.g., Nakai, H. et al. (2000) Nat. Biotechnol. 18:527–532; Sun, L. (2000) Nat. Med. 6: 599–602 (2000); Ghosh, A., et al. (2008) Mol. Ther. 16:124–130 (2008); Lai, Y (2005) Nat. Biotechnol. 23:1435–1439; Chew, W. L. et al. (2016) Nat. Methods 13:868–874; Li, J. (2008) Hum. Gene Ther. 19:958–964, each of which reference is incorporated herein in its entirety by reference.

[01162] Dual AAV vector strategies to transfer of a large gene into target cells have been described, which rely on different mechanisms including, but not limited to, trans-splicing, including overlapping regions in the dual vectors, and a hybrid of the two (see, e.g., Tornabene and Trapani (2020) Human Gene Ther. 31:47 56; see also U.S. Patent No. 8,236,557, each of which is incorporated herein by reference in its entirety).

[01163] A trans-splicing approach takes advantage of the ability of AAV ITR sequences to concatemerized to reconstitute full-length genomes, wherein each of two or more viral capsids respectively encapsulate one of two or more transfer plasmids, each of which transfer plasmid comprises a portion of the gene of interest. For example, in a dual vector approach, the two transfer plasmids may be designed as follows: the 5'-transfer plasmid comprises the promoter, the 5' portion of the coding sequence of the gene of interest, and a splicing donor (SD) signal; the 3'-transfer plasmid comprises a splicing acceptor (SA) signal, the 3' portion of the gene of interest, and the polyA signal. Upon tail-to-head ITR-mediated concatemerization of the two AAV genomes, the SD and SA signals will allow splicing of the recombined genome.

[01164] A large gene of interest is also split when taking an overlapping region approach. In the overlapping region approach, the 5' and 3' portions (and thus the 5' transfer plasmid and 3' transfer plasmid) share a recombinogenic sequence, e.g., region of homology, e.g., each portion comprises an overlapping sequence. The gene of interest is made whole in a targeted cell via homologous recombination mediated by the recombinogenic sequence, e.g., homology/overlapping region.

[01165] In a hybrid approach, the 5'-transfer plasmid and 3'-transfer plasmid each comprise a highly recombinogenic sequence, wherein the recombinogenic sequence is placed downstream of an SD signal of a 5' portion of the coding sequence of the gene of interest and upstream of an SA signal of a 3' portion of the coding sequence of the gene of interest. In this hybrid system, the gene of interest may be made whole either via ITR-mediated concatemerization and splicing and/or by homologous recombination.

[01166] Trans-splicing at the RNA or protein levels may also be utilized. In an RNA trans-splicing approach, two transfer plasmids may respectively encode for 5' and 3' fragments of the pre-mRNA of a large gene and share an intronic hybridization domain that can favor trans splicing, leading to joining of the two half-transcripts into an intact full-length mRNA.

[01167] Protein trans-splicing occurs post-translationally and is catalyzed by intervening proteins called split-inteins. Split-inteins are expressed as two independent polypeptides (N-intein and C-intein) at the extremities of two host proteins. The N-intein and C-intein polypeptides remain catalytically inactive until they encounter each other. Upon encountering each other, each intein precisely excises itself from the host protein while mediating ligation of the N- and C- host polypeptides via a peptide bond. Split-intein use has been used in AAV-based delivery of therapeutic genes of interest in muscle, liver, and retinal diseases. For example, on co-delivery of two halves of the mini-dystrophin cDNA fused to N- and C-intein coding sequences, efficient production of the two polypeptides was shown (see, e.g., Li et al. (2008) Hum Gene Ther 19:958-64).

[01168] The above dual vector approaches are well-known in the art. See, e.g., Tornabene and Trapani (2020), supra; U.S. Patent No. 8,236,557, incorporated by reference in its entirety for all purposes. Thus, in some embodiments, a modified viral capsid described herein encapsulates a nucleotide of interest, wherein the nucleotide of interest comprises a portion of a gene of interest. In some embodiments, a nucleotide of interest comprising a portion of a gene of interest further comprises a splicing donor signal or a splicing acceptor signal and/or a recombinogenic sequence. In some embodiments, a nucleotide of interest comprising a portion of a gene of interest comprises an intronic hybridization domain encoding sequence. In some embodiments, a nucleotide of interest comprising a portion of a gene of interest comprises a N-intein or C-intein encoding sequence.

[01169] Design of the transfer plasmid/nucleotide of interest encompasses including one or more regulatory elements, e.g., promoter and/or enhancer elements, that can control expression of the gene of interest. Non-limiting examples of useful promoters include, e.g., cytomegalovirus (CMV)-promoter, the spleen focus forming virus (SFFV)-promoter, the elongation factor 1 alpha (EF1a)-promoter (the 1.2 kb EFla-promoter or the 0.2 kb EFla-promoter), the chimeric EF 1 a/IF4-promoter, and the phospho-glycerate kinase (PGK)-promoter. An internal enhancer may also be present in the viral construct to increase expression of the gene of interest. For example, the CMV enhancer (Karasuyama et al. 1989. J. Exp. Med. 169:13, which is incorporated herein by reference in its entirety) may be used. In some embodiments, the CMV enhancer can be used in combination with the chicken β-actin promoter. In some embodiments,

tissue specific regulatory elements, e.g., a tissue specific promoter and/or regulatory element may be used to drive the expression of the gene of interest. For example, the use of muscle-specific regulatory elements based on the muscle creatine kinase gene has been employed for muscle gene therapy treatments, such as Duchenne muscular dystrophy (DMD) and limb-girdle muscular dystrophy (LGMD). See, e.g., Salva, M. Z. et al. (2007) Mol. Ther. 15: 320–329, incorporated herein in its entirety by reference. In some embodiments, a transfer plasmid and/or nucleotide of interest herein comprises an enhancer and/or promoter of muscle creatine kinase (MCK), wherein the enhancer and/or promoter of MCK drives expression of the gene of interest. In some embodiments, a transfer plasmid and/or nucleotide of interest herein comprises an enhancer and/or promoter element that recruits RNA Polymerase II, wherein the enhancer and/or promoter of MCK drives expression of the gene of interest. In some embodiments, a transfer plasmid and/or nucleotide of interest herein comprises an enhancer and/or promoter element that recruits RNA Polymerase III, wherein the enhancer and/or promoter of MCK drives expression of the gene of interest.

[01170] In some embodiments, bidirectional promoters vectors have also been employed for delivery of dual therapeutic gene cassettes. An example of this is the bidirectional chicken β-actin ubiquitous promoter that drives the simultaneous expression of the hexosaminidase α- and β-subunits of the HexA enzyme, the two respective genes involved in Tay-Sachs and Sandhoff diseases. Lahey, et al. (2020) Mol. Ther. 28: 2150–2160, incorporated herein in its entirety by reference. In some embodiments, a transfer plasmid and/or nucleotide of interest herein comprises a bidirectional promoter, wherein the bidirectional promoter drives the expression of two different genes of interest

[01171] A variety of reporter genes (or detectable moieties) can be encapsidated in a multimeric structure comprising the modified viral capsid proteins described herein. Exemplary reporter genes include, for example, β-galactosidase (encoded lacZ gene), Green Fluorescent Protein (GFP), enhanced Green Fluorescent Protein (eGFP), MmGFP, blue fluorescent protein (BFP), enhanced blue fluorescent protein (eBFP), mPlum, mCherry, tdTomato, mStrawberry, J-Red, DsRed, mOrange, mKO, mCitrine, Venus, YPet, yellow fluorescent protein (YFP), enhanced yellow fluorescent protein (eYFP), Emerald, CyPet, cyan fluorescent protein (CFP), Cerulean, T-Sapphire, luciferase, alkaline phosphatase, or a combination thereof. The methods described herein demonstrate the construction of targeting particles that employ the use of a reporter gene that encodes green fluorescent protein, however, persons of skill upon reading this disclosure will understand that the viral capsids described herein can be generated in the absence of a reporter gene or with any reporter gene known in the art.

[01172] A variety of therapeutic genes can also be encapsidated in a multimeric structure comprising the modified viral capsid proteins described herein, e.g., as part of a transfer particle. Non-limiting examples of a therapeutic gene include those that encode a toxin (e.g., a suicide gene), a therapeutic antibody or fragment thereof, antisense RNA, siRNA, shRNA, etc.

[01173] In some embodiments, modifications described herein may pertain to the association (e.g., display, operable linkage, binding) of a targeting ligand to a modified capsid protein and/or capsid comprising a modified capsid protein. In some embodiments, a targeting ligand can bind a surface protein expressed by a mammalian muscle cell, e.g., a protein that is expressed on the surface of a mammalian muscle cell, e.g., a mammalian muscle cell-specific surface protein.

[01174] In various embodiments, viral particles as described herein can be particularly suited for the targeted introduction of a nucleotide of interest specifically to a target cell since the viral capsid or viral capsid protein(s) can comprise a targeting ligand that binds a cell-specific surface protein of the target cell. In some embodiments, a viral capsid or viral capsid protein comprises a first member of a binding pair, associated with its cognate second member of the binding pair, and the second member is linked (e.g., fused to) a targeting ligand that binds a cell-specific surface protein. In some embodiments, the targeting ligand is operably linked to the second member, e.g., fused to the second member, optionally via a linker. In some embodiments, a targeting ligand may be a binding moiety, e.g., a natural ligand, antibody, a multispecific binding molecule, etc. In some embodiments, the targeting ligand is an antibody or portion thereof. In some embodiments, the targeting ligand is an antibody comprising a variable domain that binds a cell-specific surface protein on a target cell and a heavy chain constant domain. In some embodiments, the targeting ligand is an antibody comprising a variable domain that binds a cell-specific surface protein on a target cell and an IgG heavy chain constant domain. In some embodiments, the targeting ligand is an antibody comprising a variable domain that binds a cell-specific surface protein on a target cell and an IgG heavy chain constant domain, wherein the IgG heavy chain constant domain is operably linked, e.g., via a linker, to a protein (e.g., second member of a protein:protein binding pair) that forms an isopeptide covalent bond with the first member. In some embodiments, a capsid protein described herein comprises a first member comprising SpyTag operably linked to the viral capsid protein, and covalently linked to the SpyTag, an second member comprising SpyCatcher linked to a targeting ligand comprising an antibody variable domain and an IgG heavy chain domain, wherein SpyCatcher and the IgG heavy chain domain are linked via an amino acid linker.

[01175] Non-limiting examples of targeting ligands include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb

fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "targeting ligand," as used herein. In non-limiting embodiments, a targeting ligand useful for retargeting viral capsids as described herein comprise comprises an scFv.

[01176] In some embodiments, a targeting ligand that binds a mammalian cell-specific surface protein may be associated with (e.g., displayed by, operably linked to, bound to) a modified AAV capsid protein and resulting AAV capsids according to indirect recombinatorial approaches, wherein the AAV capsid protein is modified to comprise a first member of a binding pair (e.g., a heterologous scaffold), and optionally wherein the first member of the binding pair is linked to (e.g., covalently or non-covalently bound to) a second cognate member of the binding pair (e.g., an adaptor), further optionally wherein the second cognate member of the binding pair is fused to the targeting ligand. Non-limiting and exemplary binding pairs are listed in Buning and Srivastava (2019) *Mol. Ther. Methods Clin Dev* 12:248-265.

[01177] In some embodiments, AAV particles comprising capsid proteins retargeted to a cell-specific surface protein of a target cell may be useful in methods of treating a tissue-related disorder, with the tissue comprising the target cell. Generally, such methods comprise administering to a subject suffering from or at risk for such tissue-related disorder a viral particle or pharmaceutical composition, wherein the viral particle comprises

(i) a viral capsid modified to comprise a first member of a protein:protein binding pair,

(ii) a second member of the protein:protein binding pair, wherein the second member of the protein:protein binding pair comprises a targeting ligand that binds a cell-specific surface protein that is expressed on the surface of a target cell,

wherein the first member of the protein:protein binding pair and the second member of the protein:protein binding pair are associated to direct the tropism of the viral capsid to the muscle cell in the subject thereof, and

(iii) a nucleotide of interest encapsidated within the viral capsid.

[01178] Recombinant AAV particles comprising capsid proteins retargeted to a cell surface protein that allows the viral particles to bind a cell-specific surface protein can be useful for

delivering a delivering a nucleotide of interest, e.g., a reporter gene or a therapeutic gene, to a target cell. Non-limiting tissues that may be targeted by a modified viral capsid protein for insertion of a nucleotide of interest, e.g., a reporter gene or a therapeutic gene, include adipose tissue, blood/bone marrow, bone/cartilage/joint, brain/spinal cord/cns/bbb, breast, colon, esophagus, eye, heart, kidney, liver, lung/bronchus, lymph node, ovary, pancreas, pbmc, peripheral nervous system, placenta, prostate, rectum, skeletal muscle, skin, small intestine, spleen, stomach, testis, and uterus. Non-limiting cell types that may be targeted by a modified viral capsid protein for insertion of a nucleotide of interest, e.g., a reporter gene or a therapeutic gene, include endothelial cells, neurons (all types), oligodendrocytes (and precursors), pericytes, meninges/leptomeningeal cells, arachnoid barrier cells, peripheral glia, astrocytes, glia, schwann cells, ependymal cells, microglia, rod photoreceptor cells, muller glia cells, bipolar cells, cone photoreceptor cells, endothelial cells, cornea, sclera, optic nerve, pupillary sphincter, skeletal myocytes, fibroblasts, endothelial cells, macrophages, satellite cells, Adipocytes, fibroblasts, T-cells, Macrophages, B-cells, Dendritic cells, T-cells, B-cells, Macrophages, erythroid cells, plasmid cells, dendritic cells, glandular cells, T-cells, fibroblasts, macrophages, endothelial cells, myoepithelial cells, Adipocytes, Basal respiratory cells, respiratory cilliated cells, club cells, smooth muscle cells, ionocytes, macrophages, alveolar cells (type 1 & 2), T-cells, enothelial cells, distal enterocytes, intestinal goblet cells, undifferentiated cells, T-cells, paneth cells, B-cells, enteroednocrine cells, glandular and luminal cells, endometrial stromal cells, endothelial cells, smooth muscle cells, T-cells, macrophages, fibroblasts, squamous epithelial cells, endothelial cells, smooth muscle cells, macrophages, plasma cells, T-cells, cardiomyocytes, endothelial cells, fibroblasts, macrophages, T-cells, B-cells, Dendritic cells, proximal tubular cells, T-cells, macrophages, collecting duct cells, B-cells, glomeruli, fibroblasts, hepatocytes, B-cells, erythroid cells, B-cells, T-cells, granulosa cells, fibroblasts, smooth muscle cells, macrophages, T-cells, theca cells, fibroblasts, ductal cells, pancreatic endocrine cells, smooth muscle cells, endothelial cells, macrophages, exocrine glandular cells, monocytes, cytotrophoblasts, extravillous trophoblasts, fibroblasts, hofbauer cells, endothelial cells, basal prostatic cells, prostatic glandular cells, urothelial cells, endothelial cells, fibroblasts, smooth muscle cells, macrophages, T-cells, undifferentiated cells, intestinal goblet cells, paneth cells, distal enterocytes, enteroednocrine cells, langerhans cells, fibroblasts, endothelial cells, basal keratinocytes, suprabasal keratinocytes, T-cells, smooth muscle cells, melanocytes, monocytes, T-cells, NK-cells, dendritic cells, proximal enterocytes, undifferentiated cells, intestinal goblet cells, paneth cells, B-cells, T-cells, plasma cells, macrophages, B-cells, T-cells, gastric mucus-secreting cells, plasma cells, fibroblasts, macrophages, leydig cells, late spermatids,

spermatogonia, early spermatids, macrophages, spermatocytes, peritubular cells, sertoli cells, endothelial cells, motor neurons, sensory neurons, schwann cells, dorsal root ganglion, chondrocytes, chondroblasts, mesenchymal cells, osteoblasts and osteoclasts.

[01179] A variety of therapeutic genes can also be encapsidated in a multimeric structure comprising the capsid proteins retargeted to a cell surface protein that allows the viral particles to bind transferrin receptor 1, e.g., as part of a transfer particle. Non-limiting examples of a therapeutic gene include those that encode a toxin (e.g., a suicide gene), a therapeutic antibody or fragment thereof, antisense RNA, siRNA, shRNA, etc. As a non-limiting example, diseases and the genes which may be a nucleotide of interest and/or for which the reduction of which may be therapeutic that may be suitable for treatment using such viral particles include lysosomal storage diseases with central nervous system manifestations (neuropathic); Fabry disease, Gaucher disease, Pompe disease and many more (Genes encoding the deficient enzyme); Parkinson's/synucleinopathies (Alpha-synuclein SNCA); Parkinson's (Lrrk2); Parkinson's/Gaucher disease (GBA); FTD (Progranulin); Alzheimer's/tauopathies (3R/4R Tau, 4R-specific Tau); Alzheimer's Disease (APP/Abeta, Trem2, ApoE); ALS/FTD/TDP-43 proteinopathies (SOD1, C9orf72, TDP43, SUPT4H1, PUMA, ELOVL1, RPS25, PSMB5); Huntington's disease (HTT); Transthyretin amyloidosis (TTR); Friedreich's Ataxia (FXN); and pain (Nav1.7, Nav1.9, TrpA1, TRPM8, TrkA, FXYD2, AAK1, ASIC3, ASIC1, NGF). In some embodiments, the disease can be Tangier disease, Intellectual developmental disorder with poor growth and with or without seizures or ataxia, Hypermethioninemia due to adenosine kinase deficiency, Aspartylglycosaminuria, Fructose intolerance, hereditary, MEDNIK syndrome, Spastic paraplegia 50, autosomal recessive, Sea-blue histiocyte disease, Adenine phosphoribosyltransferase deficiency, Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI, Mucopolysaccharidosis, type X, Spinocerebellar ataxia, autosomal recessive 31, Cutis laxa, autosomal recessive, type IID, Farber disease, Hermansky-Pudlak syndrome 9, Ceroid lipofuscinosis, neuronal, 6A, Ceroid lipofuscinosis, neuronal, 6B (Kufs type), Ceroid lipofuscinosis, neuronal, 8, Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant, Galactosialidosis, cystinosis, Haim-Munk syndrome, Papillon Lefevre Syndrome, Ceroid lipofuscinosis, neuronal, 10, Pycnodysostosis, Imerslund-Grasbeck syndrome 1, Proteinuria, chronic benign], WHIM syndrome 2, Orthostatic hypotension 2, 5-fluorouracil toxicity, Dihydropyrimidine dehydrogenase deficiency, Cone-rod dystrophy 21, Vici syndrome, Arthrogryposis multiplex congenita 2, neurogenic type, Fucosidosis, Cataract 18, autosomal recessive, Pompe disease, Mucopolysaccharidosis IV, Gaucher disease, Fabry disease, Mucolipidosis II alpha/beta, Mucolipidosis III alpha/beta, Mucolipidosis III gamma,

Mucopolysaccharidosis Type VII, Tay Sachs Disease, Sandhoff disease, infantile, juvenile, and adult forms, Mucopolysaccharidosis type IIIC (Sanfilippo C), Retinitis pigmentosa 73, Hermansky-Pudlak syndrome 6, Mucopolysaccharidosis I, Mucopolysaccharidosis II, Spastic paraplegia, optic atrophy, and neuropathy, Lysosomal acid lipase defciency, Danon disease, Immunodeficiency 52, Leydig cell hypoplasia with hypergonadotropic hypogonadism, Leydig cell hypoplasia with pseudohermaphroditism, Luteinizing hormone resistance, female, Immunodeficiency, common variable, 8, with autoimmunity, Keratosis pilaris atrophicans, Chediak-Higashi syndrome, Alpha-Mannosidosis, Spondyloepiphyseal Dysplasia, Kondo-Fu Type, Mucolipidosis IV, Ceroid lipofuscinosis, neuronal, 7, Macular dystrophy with central cone involvement, Megalencephalic leukoencephalopathy with subcortical cysts, Myeloperoxidase deficiency, Deafness, autosomal recessive 2, Usher syndrome, type 1B, Kanzaki disease, Schindler disease, type I, Schindler disease, type III, Niemann-Pick disease, type C1, Niemann-Pick disease, type D, Niemann-pick disease, type C2, Spastic paraplegia 45, autosomal recessive, Sialidosis, Parkinson disease 6, early onset, Osteopetrosis, autosomal recessive 6, Hemophagocytic lymphohistiocytosis, familial, 2, Epilepsy, progressive myoclonic 4, with or without renal failure, Mucopolysaccharidosis type IIIA (Sanfilippo A), Neurodevelopmental disorder with cardiomyopathy, spasticity, and brain abnormalities, Histiocytosis-lymphadenopathy plus syndrome, Niemann-Pick disease, type A/B, acid sphingomyelinase deficiency, Congenital disorder of glycosylation, type IIn, Spinocerebellar ataxia, autosomal recessive 20, Amyotrophic lateral sclerosis 5, juvenile, Charcot-Marie-Tooth disease, axonal, type 2X, Spastic paraplegia 11, autosomal recessive, Warburg micro syndrome 4, Dystonia 32, Leukodystrophy, hypomyelinating, 12, Choreoacanthocytosis, Arthrogryposis, renal dysfunction, and cholestasis 1, Pontocerebellar hypoplasia, type 13, Pontocerebellar hypoplasia, type 2E, Neurodevelopmental disorder with spastic quadriplegia and brain abnormalities with or without seizures, Cerebellar ataxia, mental retardation, and dysequilibrium syndrome 2, Hydrocephalus, congenital, 3, with brain anomalies, Xanthinuria, type I, Spastic paraplegia 15, autosomal recessive, Intellectual disability and myopathy syndrome, Muscular dystrophy, limb-girdle, autosomal recessive 25, Neurodevelopmental disorder with seizures and nonepileptic hyperkinetic movements, Cerebellar atrophy with seizures and variable developmental delay, Ventricular tachycardia, catecholaminergic polymorphic, 2, Lipodystrophy, congenital generalized, type 3, Arrhythmogenic right ventricular dysplasia 11, Arrhythmogenic right ventricular dysplasia 11 with mild palmoplantar keratoderma and woolly hair, Cardiomyopathy, dilated, with woolly hair and keratoderma, Epidermolysis bullosa, lethal acantholytic, Skin fragility-woolly hair syndrome, Congenital heart defects, multiple types, 5, Hemolytic anemia due

to glutathione peroxidase deficiency, Naxos disease, Jervell and Lange-Nielsen syndrome 2, Myopathy, myofibrillar, 12, infantile-onset, with cardiomyopathy, Cardiomyopathy, hypertrophic, 8, Nephrotic syndrome, type 22, Developmental and epileptic encephalopathy 52, Dicarboxylic aminoaciduria, Lichtenstein-Knorr syndrome, Hypogonadotropic hypogonadism 11 with or without anosmia, Segawa syndrome, recessive, Intellectual developmental disorder with poor growth and with or without seizures or ataxia, Spondyloepimetaphyseal dysplasia, aggrecan type, Neurodevelopmental disorder with hypotonia, microcephaly, and seizures, Microcephaly 16, primary, autosomal recessive, Spinocerebellar ataxia, autosomal recessive 31, Acromesomelic dysplasia 3, Elsahy-Waters syndrome, Ceroid lipofuscinosis, neuronal, 8, Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant, Pitt-Hopkins like syndrome 1, Gaze palsy, familial horizontal, with progressive scoliosis, 2, Short-rib thoracic dysplasia 3 with or without polydactyly, Bleeding disorder, platelet-type, 22, Macrocephaly, dysmorphic facies, and psychomotor retardation, Charcot-Marie-Tooth disease, axonal, type 2S, Neuronopathy, distal hereditary motor, type VI, SESAME syndrome, Goldberg-Shprintzen megacolon syndrome, Obesity, morbid, due to leptin deficiency, Spastic paraplegia 75, autosomal recessive, Hypogonadotropic hypogonadism 27 without anosmia, Seckel syndrome 7, Pitt-Hopkins-like syndrome 2, Oxoglutarate dehydrogenase deficiency, Myopathy, congenital, progressive, with scoliosis, Epilepsy, progressive myoclonic, 10, Lissencephaly 2 (Norman-Roberts type), Thyroid hormone metabolism, abnormal, Thyroid hormone metabolism, abnormal, 1, Neuropathy, hereditary motor and sensory, type VIB, Pontocerebellar hypoplasia, type 1E, Amyotrophic lateral sclerosis 5, juvenile, Charcot-Marie-Tooth disease, axonal, type 2X, Spastic paraplegia 11, autosomal recessive, Netherton syndrome, Joubert syndrome 13, Microphthalmia, syndromic 11, Osteogenesis imperfecta, type XV, Intellectual developmental disorder with poor growth and with or without seizures or ataxia, Microcornea, myopic chorioretinal atrophy, and telecanthus, Microphthalmia, isolated 8, Fructose intolerance, hereditary, Alstrom syndrome, Sea-blue histiocyte disease, Mucopolysaccharidosis, type X, Cutis laxa, autosomal recessive, type IID, Bardet-Biedl syndrome 4, Bardet-Biedl syndrome 7, Acromesomelic dysplasia 3, Cone-rod synaptic disorder, congenital nonprogressive, Joubert syndrome 5, Leber congenital amaurosis 10, Meckel syndrome 4, Senior-Loken syndrome 6, Complement factor D deficiency, Ceroid lipofuscinosis, neuronal, 8, Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant, Achromatopsia 2, Focal segmental glomerulosclerosis 9, Ventriculomegaly with cystic kidney disease, Leber congenital amaurosis 7, Cataract 22, Galactosialidosis, Ceroid lipofuscinosis, neuronal, 10, Pycnodysostosis, Imerslund-Grasbeck syndrome 1, Proteinuria, chronic benign], WHIM syndrome 2, Cone-rod dystrophy 21, Vici

syndrome, Bleeding disorder, platelet-type, 22, Anterior segment dysgenesis 2, multiple subtypes, Fucosidosis, Cataract 18, autosomal recessive, Ectodermal dysplasia/short stature syndrome, Night blindness, congenital stationary (complete), 1B, autosomal recessive, Growth hormone deficiency with pituitary anomalies, Pituitary hormone deficiency, combined, 5, Septooptic dysplasia, Sandhoff disease, infantile, juvenile, and adult forms, Mucopolysaccharidosis type IIIC (Sanfilippo C), Retinitis pigmentosa 73, Hermansky-Pudlak syndrome 6, Cerebellar atrophy, developmental delay, and seizures, Cornea plana 2, autosomal recessive, Spastic paraplegia, optic atrophy, and neuropathy, Poretti-Boltshauser syndrome, Cortical malformations, occipital, Leydig cell hypoplasia with hypergonadotropic hypogonadism, Leydig cell hypoplasia with pseudohermaphroditism, Luteinizing hormone resistance, female, Immunodeficiency, common variable, 8, with autoimmunity, Microphthalmia/coloboma and skeletal dysplasia syndrome, Charcot-Marie-Tooth disease, axonal, type 2A2B, Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain abnormalities, Ceroid lipofuscinosis, neuronal, 7, Macular dystrophy with central cone involvement, Megalencephalic leukoencephalopathy with subcortical cysts, Myeloperoxidase deficiency, Kanzaki disease, Schindler disease, type I, Schindler disease, type III, Niemann-Pick disease, type C1, Niemann-Pick disease, type D, Niemann-pick disease, type C2, Joubert syndrome 4, Nephronophthisis 1, juvenile, Senior-Loken syndrome-1, Microcephalic osteodysplastic primordial dwarfism, type II, Retinitis pigmentosa 43, Retinitis pigmentosa-40, Cataract 11, multiple types, Cataract 11, syndromic, autosomal recessive, Osteopetrosis, autosomal recessive 6, Hemophagocytic lymphohistiocytosis, familial, 2, Microphthalmia, isolated 6, Anterior segment dysgenesis 7, with sclerocornea, Martsolf syndrome 2, Warburg micro syndrome 1, Retinal dystrophy, iris coloboma, and comedogenic acne syndrome, Leber congenital amaurosis 12, COACH syndrome 3, Joubert syndrome 7, Meckel syndrome 5, Intellectual developmental disorder and retinitis pigmentosa, Epilepsy, progressive myoclonic 4, with or without renal failure, Mucopolysaccharidosis type IIIA (Sanfilippo A), Dicarboxylic aminoaciduria, Histiocytosis-lymphadenopathy plus syndrome, Congenital disorder of glycosylation, type IIn, Heart and brain malformation syndrome, Microphthalmia with limb anomalies, Spinocerebellar ataxia, autosomal recessive 20, Deafness, autosomal recessive 115, Warburg micro syndrome 4, Segawa syndrome, recessive, Night blindness, congenital stationary (complete), 1C, autosomal recessive, Focal facial dermal dysplasia 3, Setleis type, Deafness, autosomal recessive 18A, Usher syndrome, type 1C, Microphthalmia, syndromic 11, Dystonia 32, Leukodystrophy, hypomyelinating, 12, Choreoacanthocytosis, Arthrogryposis, renal dysfunction, and cholestasis 1, Neurodevelopmental disorder with spastic quadriplegia

and brain abnormalities with or without seizures, Cerebellar ataxia, mental retardation, and dysequilibrium syndrome 2, Hydrocephalus, congenital, 3, with brain anomalies, Spastic paraplegia 15, autosomal recessive, Deafness, autosomal recessive 44, Microcephaly 5, primary, autosomal recessive, Spinocerebellar ataxia, autosomal recessive 31, Bardet-Biedl syndrome 2, Retinitis pigmentosa 74, Bardet-Biedl syndrome 4, Pitt-Hopkins like syndrome 1, Joubert syndrome 17, Orofaciodigital syndrome VI, Oculocutaneous albinism, type VIII, Hermansky-Pudlak syndrome 7, Short-rib thoracic dysplasia 3 with or without polydactyly, Macrocephaly, dysmorphic facies, and psychomotor retardation, Growth hormone deficiency with pituitary anomalies, Pituitary hormone deficiency, combined, 5, Septooptic dysplasia, Intellectual developmental disorder, autosomal recessive 57, Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain abnormalities, Hypogonadotropic hypogonadism 27 without anosmia, Pitt-Hopkins-like syndrome 2, Oxoglutarate dehydrogenase deficiency, Microcephalic osteodysplastic primordial dwarfism, type II, Intellectual developmental disorder with paroxysmal dyskinesia or seizures, Neurodevelopmental disorder with dysmorphic features, spasticity, and brain abnormalities, Developmental and epileptic encephalopathy 12, Martsolf syndrome 2, Warburg micro syndrome 1, Lissencephaly 2 (Norman-Roberts type), COACH syndrome 3, Joubert syndrome 7, Meckel syndrome 5, Thyroid hormone metabolism, abnormal, Thyroid hormone metabolism, abnormal, 1, Neuropathy, hereditary motor and sensory, type VIB, Pontocerebellar hypoplasia, type 1E, Spinocerebellar ataxia, autosomal recessive 14, Microcephaly-capillary malformation syndrome, Neurodevelopmental disorder, nonprogressive, with spasticity and transient opisthotonus, Intellectual developmental disorder, autosomal recessive 13, Microcephaly 2, primary, autosomal recessive, with or without cortical malformations, Osteogenesis imperfecta, type XV, Diarrhea 9, Neurodevelopmental disorder with hypotonia, microcephaly, and seizures, Ceroid lipofuscinosis, neuronal, 8, Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant, Nephrotic syndrome, type 24, Gaze palsy, familial horizontal, with progressive scoliosis, 2, Short-rib thoracic dysplasia 3 with or without polydactyly, Charcot-Marie-Tooth disease, axonal, type 2S, Neuronopathy, distal hereditary motor, type VI, Myopathy, congenital, progressive, with scoliosis, Neu-Laxova syndrome 1, Phosphoglycerate dehydrogenase deficiency, Carpenter syndrome, Lissencephaly 2 (Norman-Roberts type), Joubert syndrome 13, Cerebellar hypoplasia and mental retardation with or without quadrupedal locomotion 1, Osteogenesis imperfecta, type XV, Visceral neuropathy, familial, 2, autosomal recessive, Arthrogryposis multiplex congenita 1, neurogenic, with myelin defect, Multicentric osteolysis, nodulosis, and arthropathy, Charcot-Marie-Tooth disease, type 4D, Hypogonadotropic hypogonadism 27 without anosmia, Charcot-Marie-Tooth disease, type

4C, Neuropathy, hereditary motor and sensory, type VIB, Pontocerebellar hypoplasia, type 1E, Encephalopathy, progressive, with amyotrophy and optic atrophy, Hypoparathyroidism-retardation-dysmorphism syndrome, Kenny-Caffey syndrome, type 1, Brody myopathy, Muscular dystrophy, limb-girdle, autosomal recessive 25, Lipodystrophy, congenital generalized, type 3, Myasthenic syndrome, congenital, 1B, fast-channel, Myasthenic syndrome, congenital, 3B, fast-channel, Myasthenic syndrome, congenital, 3C, associated with acetylcholine receptor deficiency, Ceroid lipofuscinosis, neuronal, 8, Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant, Spondylocarpotarsal synostosis syndrome, Hemolytic anemia due to glutathione peroxidase deficiency, Gillespie syndrome, Nemaline myopathy 10, Myopathy, congenital, progressive, with scoliosis, Myasthenic syndrome, congenital, 16, Dystonia, dopa-responsive, due to sepiapterin reductase deficiency, Split-hand/foot malformation 6, Spondyloepimetaphyseal dysplasia, aggrecan type, Bardet-Biedl syndrome 2, Retinitis pigmentosa 74, Acromesomelic dysplasia 3, Osteochondrodysplasia, brachydactyly, and overlapping malformed digits, Temtamy preaxial brachydactyly syndrome, Fibrochondrogenesis 1, Deafness, autosomal recessive 53, Fibrochondrogenesis 2, Otospondylomegaepiphyseal dysplasia, autosomal recessive, Steel syndrome, Pycnodysostosis, Spondyloepimetaphyseal dysplasia, Shohat type, Acromesomelic dysplasia 2A, Acromesomelic dysplasia 2B, Acromesomelic dysplasia 2C, Hunter-Thompson type, Brachydactyly, type A1, C, Leber congenital amaurosis 17, Short-rib thoracic dysplasia 2 with or without polydactyly, Obesity, morbid, due to leptin deficiency, Neurodevelopmental disorder with epilepsy and hypoplasia of the corpus callosum, Myopathy, congenital, progressive, with scoliosis, Rhizomelic limb shortening with dysmorphic features, Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis, Hypoparathyroidism, familial isolated 1, Robinow syndrome, autosomal recessive, Spondyloepimetaphyseal dysplasia, Krakow type, Congenital disorder of glycosylation, type IIn, Waardenburg syndrome, type 2D, Ehlers-Danlos syndrome, cardiac valvular type, Steel syndrome, Factor VII deficiency, Short-rib thoracic dysplasia 2 with or without polydactyly, Keratosis pilaris atrophicans, Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis, Nephrotic syndrome, type 14, Waardenburg syndrome, type 2D, Cone-rod dystrophy 3, Fundus flavimaculatus, Retinal dystrophy, early-onset severe, Retinitis pigmentosa 19, Stargardt disease 1, Lethal congenital contracture syndrome 8, Nephronophthisis 16, Distal renal tubular acidosis 3, with or without sensorineural hearing loss, Distal renal tubular acidosis 2 with progressive sensorineural hearing loss, Bardet-Biedl syndrome 2, Retinitis pigmentosa 74, Deafness, autosomal recessive 93, Cone-rod synaptic disorder, congenital nonprogressive, Joubert syndrome 5, Leber congenital amaurosis 10,

Meckel syndrome 4, Senior-Loken syndrome 6, Bartter syndrome, type 3, Deafness, autosomal recessive 103, Ceroid lipofuscinosis, neuronal, 6A, Ceroid lipofuscinosis, neuronal, 6B (Kufs type), Ceroid lipofuscinosis, neuronal, 8, Ceroid lipofuscinosis, neuronal, 8, Northern epilepsy variant, Retinitis pigmentosa 61, Usher syndrome, type 3A, Achromatopsia 2, Fibrochondrogenesis 1, Joubert syndrome 17, Orofaciodigital syndrome VI, Leber congenital amaurosis 7, Cataract 22, Chronic granulomatous disease 4, autosomal recessive, Cone-rod dystrophy 21, Short-rib thoracic dysplasia 3 with or without polydactyly, Leber congenital amaurosis 17, Hyperekplexia 2, Night blindness, congenital stationary (complete), 1B, autosomal recessive, Immunodeficiency-centromeric instability-facial anomalies syndrome 4, Muscular dystrophy, congenital, with cataracts and intellectual disability, Renal hypodysplasia/aplasia 1, SESAME syndrome, Cerebellar atrophy, developmental delay, and seizures, Pseudohypoaldosteronism, type IID, Cortical malformations, occipital, Leber congenital amaurosis 14, Retinal dystrophy, early-onset severe, Retinitis pigmentosa, juvenile, Night blindness, congenital stationary (complete), 1F, autosomal recessive, Metaphyseal anadysplasia 2, Deafness, autosomal recessive 30, Deafness, autosomal recessive 2, Usher syndrome, type 1B, Short-rib thoracic dysplasia 6 with or without polydactyly, Meckel syndrome 7, Nephronophthisis 3, Renal-hepatic-pancreatic dysplasia 1, Boudin-Mortier syndrome, Microcephalic osteodysplastic primordial dwarfism, type II, Retinitis pigmentosa 43, Retinitis pigmentosa-40, Leber congenital amaurosis 12, Bothnia retinal dystrophy, Newfoundland rod-cone dystrophy, COACH syndrome 3, Joubert syndrome 7, Meckel syndrome 5, Nephrotic syndrome, type 14, Leber congenital amaurosis 3, Retinitis pigmentosa 94, variable age at onset, autosomal recessive, Immunodeficiency 31B, mycobacterial and viral infections, autosomal recessive, Corneal dystrophy, gelatinous drop-like, Segawa syndrome, recessive, COACH syndrome 1, Joubert syndrome 6, Meckel syndrome 3, Nephronophthisis 11, RHYNS syndrome, Night blindness, congenital stationary (complete), 1C, autosomal recessive, Diarrhea 9, Nephronophthisis-like nephropathy 1, Combined oxidative phosphorylation deficiency 8, Leukoencephalopathy, progressive, with ovarian failure, 2-methylbutyrylglycinuria, Alpha-methylacetoacetic aciduria, Aicardi-Goutieres syndrome 6, Neurodevelopmental disorder with hypotonia, microcephaly, and seizures, Deafness, autosomal recessive 44, Obesity, susceptibility to, BMIQ19}, Lethal congenital contracture syndrome 8, Hypermethioninemia due to adenosine kinase deficiency, Neurodegeneration, childhood-onset, stress-induced, with variable ataxia and seizures, Alopecia-intellectual disability syndrome 1, Immunodeficiency with hyper-IgM, type 2, Leukodystrophy, hypomyelinating, 3, Autoimmune polyendocrinopathy syndrome, type I, with or without reversible metaphyseal dysplasia, Spermatogenic failure 27,

Glycogen storage disease XII, Fructose intolerance, hereditary, Intellectual developmental disorder, autosomal recessive 71, Myopathy due to myoadenylate deaminase deficiency, Pontocerebellar hypoplasia, type 9, Spastic paraplegia 63, Ferguson-Bonni neurodevelopmental syndrome, Scott syndrome, Spastic paraplegia 48, autosomal recessive, Adenine phosphoribosyltransferase deficiency, Ataxia, early-onset, with oculomotor apraxia and hypoalbuminemia, Spinal muscular atrophy with congenital bone fractures 2, Cutis laxa, autosomal recessive, type IID, Distal renal tubular acidosis 2 with progressive sensorineural hearing loss, Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies, type A, 11, Bile acid conjugation defect 1, Agammaglobulinemia 4, Hermansky-Pudlak syndrome 9, Acromesomelic dysplasia 3, Erythrocytosis, familial, 8, Fanconi anemia, complementation group J, Desbuquois dysplasia 1, Epiphyseal dysplasia, multiple, 7, Immunodeficiency 11A, Immunodeficiency, common variable, 3, Lymphoproliferative syndrome 2, Immunodeficiency with hyper-IgM, type 3, Deafness, autosomal recessive 32, with or without immotile sperm, Microcephaly 12, primary, autosomal recessive, Microcephaly 13, primary, autosomal recessive, Nephronophthisis 15, Complement factor B deficiency, Cocoon syndrome, Popliteal pterygium syndrome, Bartsocas-Papas type 2, Cold-induced sweating syndrome 2, Leukodystrophy, hypomyelinating, 20, Pitt-Hopkins like syndrome 1, Neurodegeneration with brain iron accumulation 6, Pontocerebellar hypoplasia, type 12, Carbamoylphosphate synthetase I deficiency, Surfactant metabolism dysfunction, pulmonary, 5, Neutropenia, severe congenital, 7, autosomal recessive, Joubert syndrome 21, Cerebroretinal microangiopathy with calcifications and cysts, Microcephaly, facial dysmorphism, renal agenesis, and ambiguous genitalia syndrome, WHIM syndrome 2, Aromatase deficiency, Bile acid synthesis defect, congenital, 3, Spastic paraplegia 5A, autosomal recessive, Developmental and epileptic encephalopathy 86, Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation, Oculocutaneous albinism, type VIII, Pentosuria], Aromatic L-amino acid decarboxylase deficiency, Mitochondrial DNA depletion syndrome 3 (hepatocerebral type), Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive 4, Miller syndrome, Pyruvate dehydrogenase E2 deficiency, Systemic lupus erythematosus 16, Immunodeficiency-centromeric instability-facial anomalies syndrome 1, Immunodeficiency 40, Congenital disorder of glycosylation, type Ie, 5-fluorouracil toxicity, Dihydropyrimidine dehydrogenase deficiency, Intellectual developmental disorder, autosomal recessive 50, Combined oxidative phosphorylation deficiency 17, Dysautonomia, familial, Spastic paraplegia 64, autosomal recessive, Bleeding disorder, platelet-type, 22, Eosinophil peroxidase deficiency], Visceral neuropathy, familial, 2, autosomal recessive, Fanconi anemia, complementation group

Q, XFE progeroid syndrome, Xeroderma pigmentosum, group F, Xeroderma pigmentosum, type F/Cockayne syndrome, Cerebrooculofacioskeletal syndrome 3, Xeroderma pigmentosum, group G, Xeroderma pigmentosum, group G/Cockayne syndrome, Cockayne syndrome, type A, UV-sensitive syndrome 2, Deafness, autosomal recessive 109, Pontocerebellar hypoplasia, type 1F, Dysprothrombinemia, Hypoprothrombinemia, Immunodeficiency 90 with encephalopathy, functional hyposplenia, and hepatic dysfunction, Raine syndrome, Fanconi anemia, complementation group D2, Fanconi anemia, complementation group I, Fanconi anemia, complementation group L, Peroxisomal fatty acyl-CoA reductase 1 disorder, Combined oxidative phosphorylation deficiency 14, Spastic paraplegia 77, autosomal recessive, Rajab interstitial lung disease with brain calcifications 2, Combined oxidative phosphorylation deficiency 44, Parkinson disease 15, autosomal recessive, Leukocyte adhesion deficiency, type III, Siddiqi syndrome, Anterior segment dysgenesis 2, multiple subtypes, T-cell immunodeficiency, congenital alopecia, and nail dystrophy, Combined oxidative phosphorylation deficiency 41, Glutaricaciduria, type I, Diabetes mellitus, permanent neonatal 1, Bleeding disorder, platelet-type, 17, Nonaka myopathy, Hypertriglyceridemia, transient infantile, Chudley-McCullough syndrome, Jaberi-Elahi syndrome, Combined oxidative phosphorylation deficiency 23, Vertebral, cardiac, renal, and limb defects syndrome 1, T-cell lymphoma, subcutaneous panniculitis-like, Immunodeficiency-centromeric instability-facial anomalies syndrome 4, Hemochromatosis, type 2A, Heme oxygenase-1 deficiency, Dystonia 2, torsion, autosomal recessive, D-bifunctional protein deficiency, Perrault syndrome 1, Premature ovarian failure 19, Immunodeficiency 27A, mycobacteriosis, AR, Charcot-Marie-Tooth disease, axonal, type 2S, Neuronopathy, distal hereditary motor, type VI, Immunodeficiency 15B, Immunodeficiency 29, mycobacteriosis, Immunodeficiency 30, Candidiasis, familial, 9, Immunodeficiency, common variable, 11, Immunodeficiency 56, Immunodeficiency 41 with lymphoproliferation and autoimmunity, Immunodeficiency 63 with lymphoproliferation and autoimmunity, Immunodeficiency 39, Immunodeficiency 32B, monocyte and dendritic cell deficiency, autosomal recessive, Autoimmune disease, multisystem, with facial dysmorphism, Lymphoproliferative syndrome 1, Muscular dystrophy, limb-girdle, autosomal recessive 27, SCID, autosomal recessive, T-negative/B-positive type, Basal ganglia calcification, idiopathic, 8, autosomal recessive, Hemorrhagic destruction of the brain, subependymal calcification, and cataracts, Hydroxykynureninuria, Vertebral, cardiac, renal, and limb defects syndrome 2, Immunodeficiency 52, Immunodeficiency 81, Obesity, morbid, due to leptin deficiency, Obesity, morbid, due to leptin receptor deficiency, Lipodystrophy, familial partial, type 6, Chediak-Higashi syndrome, 3-Methylcrotonyl-CoA carboxylase 2 deficiency, Basel-Vanagait-Smirin-Yosef

syndrome, Intellectual developmental disorder, autosomal recessive 72, Mitochondrial DNA depletion syndrome 11, Mismatch repair cancer syndrome 1, Metaphyseal anadysplasia 2, Xanthinuria, type II, Molybdenum cofactor deficiency B, Thrombocytopenia, anemia, and myelofibrosis, Deafness, autosomal recessive 111, Familial adenomatous polyposis 4, Premature ovarian failure 13, Vertebral, cardiac, renal, and limb defects syndrome 3, Encephalopathy, progressive, early-onset, with brain edema and/or leukoencephalopathy, Infantile liver failure syndrome 2, Short stature, optic nerve atrophy, and Pelger-Huet anomaly, Microcephaly 22, primary, autosomal recessive, Chronic granulomatous disease 1, autosomal recessive, Chronic granulomatous disease 2, autosomal recessive, Charcot-Marie-Tooth disease, type 4D, Mitochondrial complex I deficiency, nuclear type 22, Mitochondrial complex I deficiency, nuclear type 37, Mitochondrial complex I deficiency, nuclear type 32, Mitochondrial complex I deficiency, nuclear type 24, Mitochondrial complex I deficiency, nuclear type 5, Dyskeratosis congenita, autosomal recessive 2, Glucocorticoid deficiency 4, with or without mineralocorticoid deficiency, Acromesomelic dysplasia 1, Maroteaux type, Boudin-Mortier syndrome, Spastic paraplegia 45, autosomal recessive, Insensitivity to pain, congenital, with anhidrosis, Striatonigral degeneration, infantile, Nephrotic syndrome, type 17, Oxoglutarate dehydrogenase deficiency, Hyperphenylalaninemia, non-PKU mild], Phenylketonuria, Parkinson disease 7, autosomal recessive early-onset, Myopathy, congenital, progressive, with scoliosis, Intellectual developmental disorder with paroxysmal dyskinesia or seizures, Lacticacidemia due to PDX1 deficiency, Pancreatic agenesis 1, Neuropathy, hereditary motor and sensory, type VIC, with optic atrophy, Glycogen storage disease VII, Immunodeficiency 23, Rhizomelic limb shortening with dysmorphic features, Developmental and epileptic encephalopathy 12, Osteopetrosis, autosomal recessive 6, Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis, Mitochondrial DNA depletion syndrome 16 (hepatic type), Mitochondrial DNA depletion syndrome 16B (neuroophthalmic type), Hemophagocytic lymphohistiocytosis, familial, 2, Immunodeficiency 26, with or without neurologic abnormalities, Dystonia 16, Hypoparathyroidism, familial isolated 1, Hyperphenylalaninemia, BH4-deficient, A, Myopathy, lactic acidosis, and sideroblastic anemia 1, Intellectual developmental disorder with abnormal behavior, microcephaly, and short stature, Leukodystrophy, hypomyelinating, 10, Combined oxidative phosphorylation deficiency 40, Carpenter syndrome, Immunodeficiency 73C with defective neutrophil chemotaxis and hypogammaglobulinemia, Leber congenital amaurosis 12, Deafness, autosomal recessive 24, Aicardi-Goutieres syndrome 3, RIDDLE syndrome, Robinow syndrome, autosomal recessive, Ribose 5-phosphate isomerase deficiency, Mitochondrial complex II deficiency, nuclear type 4, Spinocerebellar ataxia, autosomal recessive, with axonal

neuropathy 2, Neurodevelopmental disorder with cardiomyopathy, spasticity, and brain abnormalities, Albinism, oculocutaneous, type VI, Skin/hair/eye pigmentation 4, fair/dark skin], Citrullinemia, adult-onset type II, Citrullinemia, type II, neonatal-onset, Congenital disorder of glycosylation, type IIn, Parkinsonism-dystonia, infantile, 1, Lichtenstein-Knorr syndrome, Heart and brain malformation syndrome, Dentin dysplasia, type I, with microdontia and misshapen teeth, Osteopetrosis, autosomal recessive 8, Ovarian dysgenesis 9, Deafness, autosomal recessive 115, Dystonia, dopa-responsive, due to sepiapterin reductase deficiency, Pyropoikilocytosis, Spherocytosis, type 3, Immunodeficiency 31B, mycobacterial and viral infections, autosomal recessive, Hemophagocytic lymphohistiocytosis, familial, 4, Intellectual developmental disorder, autosomal recessive 40, Hypertryptophanemia], Spinocerebellar ataxia, autosomal recessive, with axonal neuropathy 1, Osteogenesis imperfecta, type XVIII, Catel-Manzke syndrome, Segawa syndrome, recessive, Spinocerebellar ataxia, autosomal recessive 28, Paget disease of bone 5, juvenile-onset, Mosaic variegated aneuploidy syndrome 3, Oocyte maturation defect 9, Intellectual developmental disorder, autosomal recessive 68, Immunodeficiency 35, Beta-ureidopropionase deficiency, Leber congenital amaurosis 19, Combined oxidative phosphorylation deficiency 20, Galloway-Mowat syndrome 6, Microcephaly, growth deficiency, seizures, and brain malformations, Osteogenesis imperfecta, type XV, Split-hand/foot malformation 6, Dyskeratosis congenita, autosomal recessive 3, Xanthinuria, type I, or Spastic paraplegia 15, autosomal recessive. In some embodiments, the genes which may be a nucleotide of interest can be ABCA1, ABCA2, ADK, AGA, ALDOB, AP1S1, AP4M1, APOE, APRT, ARSB, ARSK, ATG7, ATP6V1A, ASAH1, BLOC1S6, CLN6, CLN6, CLN8, CLN8, CTSA, CTNS, CTSC, CTSD, CTSK, CUBN, CUBN, CXCR2, CYB561, DPYD, DPYD, DRAM2, EPG5, ERGIC1, FUCA1, FYCO1, GAA, GALNS, GBA, GLA, GNPTAB, GNPTAB, GNPTG, GUSB, HEXA, HEXB, HGSNAT, HGSNAT, HPS6, IDUA, IDS, KLC2, LAL, LAMP2, LAT, LHCGR, LHCGR, LHCGR, LRBA, LRP1, LYST, MAN2B1, MBTPS1, MCOLN1, MFSD8, MFSD8, MLC1, MPO, MYO7A, MYO7A, NAGA, NAGA, NAGA, NPC1, NPC1, NPC2, NT5C2, NEU1, PINK1, PLEKHM1, PRF1, SCARB2, SGSH, SHMT2, SLC29A3, SMPD1, SLC39A8, SNX14, SPG11, SPG11, SPG11, TBC1D20, VPS11, VPS11, VPS13A, VPS33B, VPS51, VPS53, WDR45B, WDR81, WDR81, XDH, ZFYVE26, ABCC9, BVES, CACNA1B, CACNA2D2, CASQ2, CAV1, DSC2, DSC2, DSP, DSP, DSP, GATA5, GPX1, JUP, KCNE1, MYL2, MYL3, NOS1AP, SCN1B, SLC1A1, SLC9A1, TACR3, TH, ABCA2, ACAN, ADARB1, ANKLE2, ATG7, BMPR1B, CDH11, CLN8, CLN8, CNTNAP2, DCC, DYNC2H1, EPHB2, HERC1, IGHMBP2, IGHMBP2, KCNJ10, KIFBP, LEP, MAG, NHLH2, NIN, NRXN1, OGDH, PAX7, PRDM8, RELN, SECISBP2, SECISBP2, SLC25A46, SLC25A46, SPG11, SPG11, SPG11, SPINK5, TCTN1, VAX1, WNT1,

ABCA2, ADAMTS18, ALDH1A3, ALDOB, ALMS1, APOE, ARSK, ATP6V1A, BBS4, BBS7, BMPR1B, CABP4, CEP290, CEP290, CEP290, CEP290, CFD, CLN8, CLN8, CNGA3, CRB2, CRB2, CRX, CRYBB3, CTSA, CTSD, CTSK, CUBN, CUBN, CXCR2, DRAM2, EPG5, EPHB2, FOXE3, FUCA1, FYCO1, GRHL2, GRM6, HESX1, HESX1, HESX1, HEXB, HGSNAT, HGSNAT, HPS6, KCNMA1, KERA, KLC2, LAMA1, LAMC3, LHCGR, LHCGR, LHCGR, LRBA, MAB21L2, MFN2, MFSD2A, MFSD8, MFSD8, MLC1, MPO, NAGA, NAGA, NAGA, NPC1, NPC1, NPC2, NPHP1, NPHP1, NPHP1, PCNT, PDE6A, PDE6B, PITX3, PITX3, PLEKHM1, PRF1, PRSS56, PXDN, RAB3GAP1, RAB3GAP1, RBP4, RD3, RPGRIP1L, RPGRIP1L, RPGRIP1L, SCAPER, SCARB2, SGSH, SLC1A1, SLC29A3, SLC39A8, SMG9, SMOC1, SNX14, SPNS2, TBC1D20, TH, TRPM1, TWIST2, USH1C, USH1C, VAX1, VPS11, VPS11, VPS13A, VPS33B, WDR45B, WDR81, WDR81, ZFYVE26, ADCY1, ASPM, ATG7, BBS2, BBS2, BBS4, CNTNAP2, CPLANE1, CPLANE1, DCT, DTNBP1, DYNC2H1, HERC1, HESX1, HESX1, HESX1, MBOAT7, MFSD2A, NHLH2, NRXN1, OGDH, PCNT, PDE2A, PGAP1, PLCB1, RAB3GAP1, RAB3GAP1, RELN, RPGRIP1L, RPGRIP1L, RPGRIP1L, SECISBP2, SECISBP2, SLC25A46, SLC25A46, SPTBN2, STAMBP, TNR, TRAPPC9, WDR62, WNT1, WNT2B, ADARB1, CLN8, CLN8, DAAM2, DCC, DYNC2H1, IGHMBP2, IGHMBP2, PAX7, PHGDH, PHGDH, RAB23, RELN, TCTN1, VLDLR, WNT1, ERBB2, LGI4, MMP2, NDRG1, NHLH2, SH3TC2, SLC25A46, SLC25A46, TBCE, TBCE, TBCE, ATP2A1, BVES, CAV1, CHRNA1, CHRND, CHRND, CLN8, CLN8, FLNB, GPX1, ITPR1, LMOD3, PAX7, SCN4A, SPR, WNT10B, ACAN, BBS2, BBS2, BMPR1B, CHST11, CHSY1, COL11A1, COL11A2, COL11A2, COL11A2, COL27A1, CTSK, DDRGK1, GDF5, GDF5, GDF5, GDF5, GDF6, IFT80, LEP, LNPK, PAX7, PKDCC, POC1A, PTH, ROR2, SIK3, SLC39A8, SNAI2, COL1A2, COL27A1, F7, IFT80, LRP1, POC1A, SGPL1, SNAI2, ABCA4, ABCA4, ABCA4, ABCA4, ABCA4, ADCY6, ANKS6, ATP6V0A4, ATP6V1B1, BBS2, BBS2, CABP2, CABP4, CEP290, CEP290, CEP290, CEP290, CLCNKB, CLIC5, CLN6, CLN6, CLN8, CLN8, CLRN1, CLRN1, CNGA3, COL11A1, CPLANE1, CPLANE1, CRX, CRYBB3, CYBA, DRAM2, DYNC2H1, GDF6, GLRB, GRM6, HELLS, INPP5K, ITGA8, KCNJ10, KCNMA1, KLHL3, LAMC3, LRAT, LRAT, LRAT, LRIT3, MMP9, MYO3A, MYO7A, MYO7A, NEK1, NPHP3, NPHP3, NPHP3, NPR3, PCNT, PDE6A, PDE6B, RD3, RLBP1, RLBP1, RPGRIP1L, RPGRIP1L, RPGRIP1L, SGPL1, SPATA7, SPATA7, STAT1, TACSTD2, TH, TMEM67, TMEM67, TMEM67, TMEM67, TMEM67, TRPM1, WNT2B, XPNPEP3, AARS2, AARS2, ACADSB, ACAT1, ADAR, ADARB1, ADCY1, ADCY3, ADCY6, ADK, ADPRS, AHSG, AICDA, AIMP1, AIRE, AK7, ALDOA, ALDOB, ALKBH8, AMPD1, AMPD2, AMPD2, ANAPC7, ANO6, AP5Z1, APRT, APTX, ASCC1, ATP6V1A, ATP6V1B1, B3GALNT2, BAAT, BLNK, BLOC1S6, BMPR1B, BPGM, BRIP1, CANT1, CANT1, CARD11, CD19, CD27,

CD40, CDC14A, CDK6, CENPE, CEP164, CFB, CHUK, CHUK, CLCF1, CNP, CNTNAP2, COASY, COASY, CPS1, CSF2RB, CSF3R, CSPP1, CTC1, CTU2, CXCR2, CYP19A1, CYP7B1, CYP7B1, DALRD3, DARS2, DCT, DCXR, DDC, DGUOK, DGUOK, DHODH, DLAT, DNASE1L3, DNMT3B, DOCK2, DPM1, DPYD, DPYD, EDC3, ELAC2, ELP1, ENTPD1, EPHB2, EPX, ERBB2, ERCC4, ERCC4, ERCC4, ERCC4, ERCC5, ERCC5, ERCC5, ERCC8, ERCC8, ESRP1, EXOSC1, F2, F2, FADD, FAM20C, FANCD2, FANCI, FANCL, FAR1, FARS2, FARS2, FARSA, FASTKD2, FBXO7, FERMT3, FITM2, FOXE3, FOXN1, GATB, GCDH, GCK, GFI1B, GNE, GPD1, GPSM2, GTPBP2, GTPBP3, HAAO, HAVCR2, HELLS, HJV, HMOX1, HPCA, HSD17B4, HSD17B4, HSF2BP, IFNGR1, IGHMBP2, IGHMBP2, IKBKB, IL12B, IL12RB1, IL17RC, IL21, IL21R, IL2RA, IL2RB, IRF7, IRF8, ITCH, ITK, JAG2, JAK3, JAM2, JAM3, KYNU, KYNU, LAT, LCP2, LEP, LEPR, LIPE, LYST, MCCC2, MED25, METTL5, MGME1, MLH1, MMP9, MOCOS, MOCS2, MPIG6B, MPZL2, MSH3, MSH5, NADSYN1, NAXE, NBAS, NBAS, NCAPD3, NCF1, NCF2, NDRG1, NDUFA10, NDUFA8, NDUFB8, NDUFB9, NDUFS1, NHP2, NNT, NPR2, NPR3, NT5C2, NTRK1, NUP62, NUP85, OGDH, PAH, PAH, PARK7, PAX7, PDE2A, PDHX, PDX1, PDXK, PFKM, PGM3, PKDCC, PLCB1, PLEKHM1, POC1A, POLG2, POLG2, PRF1, PRKDC, PRKRA, PTH, PTS, PUS1, PUS7, PYCR2, QRSL1, RAB23, RAC2, RD3, RDX, RNASEH2C, RNF168, ROR2, RPIA, SDHB, SETX, SHMT2, SLC24A5, SLC24A5, SLC25A13, SLC25A13, SLC39A8, SLC6A3, SLC9A1, SMG9, SMOC2, SNX10, SPIDR, SPNS2, SPR, SPTA1, SPTA1, STAT1, STX11, TAF2, TDO2, TDP1, TENT5A, TGDS, TH, THG1L, TNFRSF11B, TRIP13, TRIP13, TRMT1, TYK2, UPB1, USP45, VARS2, WDR4, WDR4, WNT1, WNT10B, WRAP53, XDH, or ZFYVE26.

[01180] CNS disorders and disorders with neurological symptoms amenable to gene therapy include, but are not limited to: Alzheimer's, brain cancer, Behcet's Disease, cerebral Lupus, Creutzfeldt-Jakob Disease, dementia, epilepsy, encephalitis, Friedreich's Ataxia, Guillain-Barre Syndrome, Gaucher Disease, headache, hydrocephalus, Huntington's disease, intracranial hypertension, leukodystrophy, migraine, myasthenia gravis, muscular dystrophy, multiple sclerosis, narcolepsy, neuropathy, Prader-Willi Syndrome, Parkinson's disease, Rett Syndrome, restless leg syndrome, sleep disorders, subarachnoid hemorrhage, stroke, traumatic brain injury, trigeminal neuralgia, transient ischemic attack, and Von Hippel-Lindau Syndrome (angiomatosis).

[01181] In some embodiments, a viral capsid as described herein may encapsidate a therapeutic gene in which the expression prevents, alleviates, or otherwise reduces a one or more symptoms of an enzyme-deficiency disease and/or a disease selected from the group consisting of Fabry disease, Gaucher disease, MPS I, MPS II, MPS IIIA, MPS IIIB, MPS IIID,

MPS IVB, MPS VI, MPS VII, MPS IX, Pompe disease, Lysosomal acid lipase deficiency, Metachromatic leukodystrophy, Niemann-Pick diseases types A, B, and C2, Alpha mannosidosis, Neuraminidase deficiency, Sialidosis, Aspartylglycosaminuria, Combined saposin deficiency, Atypical Gaucher disease, Farber lipogranulomatosis, Fucosidosis, and Beta mannosidosis.

[01182] "Enzyme-deficiency diseases" include non-lysosomal storage disease such as Krabbe disease (galactosylceramidase), phenylketonuria, galactosemia, maple syrup urine disease, mitochondrial disorders, Friedreich ataxia, Zellweger syndrome, adrenoleukodystrophy, Wilson disease, hemochromatosis, ornithine transcarbamylase deficiency, methylmalonic academia, propionic academia, and lysosomal storage diseases. "Lysosomal storage diseases" include any disorder resulting from a defect in lysosome function. Currently, approximately 50 lysosomal storage disorders have been identified, the most well-known of which include Tay-Sachs, Gaucher, and Niemann-Pick disease. The pathogeneses of the diseases are ascribed to the buildup of incomplete degradation products in the lysosome, usually due to loss of protein function. Lysosomal storage diseases are caused by loss-of-function or attenuating variants in the proteins whose normal function is to degrade or coordinate degradation of lysosomal contents. The proteins affiliated with lysosomal storage diseases include enzymes, receptors and other transmembrane proteins (*e.g.*, NPC1), post-translational modifying proteins (*e.g.*, sulfatase), membrane transport proteins, and non-enzymatic cofactors and other soluble proteins (*e.g.*, GM2 ganglioside activator). Thus, lysosomal storage diseases encompass more than those disorders caused by defective enzymes *per se*, and include any disorder caused by any molecular defect. Thus, as used herein, the term "enzyme" is meant to encompass those other proteins associated with lysosomal storage diseases.

[01183] The nature of the molecular lesion affects the severity of the disease in many cases, *i.e.* complete loss-of-function tends to be associated with pre-natal or neo-natal onset, and involves severe symptoms; partial loss-of-function is associated with milder (relatively) and later-onset disease. Generally, only a small percentage of activity needs to be restored to have to correct metabolic defects in deficient cells. Lysosomal storage diseases are generally described in Desnick and Schuchman, 2012.

[01184] Lysosomal storage diseases are a class of rare diseases that affect the degradation of myriad substrates in the lysosome. Those substrates include sphingolipids, mucopolysaccharides, glycoproteins, glycogen, and oligosaccharides, which can accumulate in the cells of those with disease leading to cell death. Organs affected by lysosomal storage

diseases include the central nervous system (CNS), the peripheral nervous system (PNS), lungs, liver, bone, skeletal and cardiac muscle, and the reticuloendothelial system.

[01185] Options for the treatment of lysosomal storage diseases include enzyme replacement therapy (ERT), substrate reduction therapy, pharmacological chaperone-mediated therapy, hematopoietic stem cell transplant therapy, and gene therapy. An example of substrate reduction therapy includes the use of Miglustat or Eliglustat to treat Gaucher Type 1. These drugs act by blocking synthase activity, which reduces subsequent substrate production. Hematopoietic stem cell therapy (HSCT), for example, is used to ameliorate and slow-down the negative central nervous system phenotype in subjects with some forms of MPS. See R.M. Boustany, "Lysosomal storage diseases--the horizon expands," 9(10) Nat. Rev. Neurol. 583-98, Oct. 2013; which reference is incorporated herein in its entirety by reference.

[01186] Two of the most common LSDs are Pompe disease and Fabry disease. Pompe disease, which has an estimated incidence of 1 in 10,000, is caused by defective lysosomal enzyme alpha-glucosidase (GAA), which results in the deficient processing of lysosomal glycogen. Accumulation of lysosomal glycogen occurs predominantly in skeletal, cardiac, and hepatic tissues. Infantile onset Pompe causes cardiomegaly, hypotonia, hepatomegaly, and death due to cardiorespiratory failure, usually before 2 years of age. Adult onset Pompe occurs as late as the second to sixth decade and usually involves only skeletal muscle. Treatments currently available include Genzyme's MYOZYME®/LUMIZYME® (alglucosidase alfa), which is a recombinant human alpha-glucosidase produced in CHO cells and administered by intravenous infusion.

[01187] Fabry disease, which has including mild late onset cases an overall estimated incidence of 1 in 3,000, is caused by defective lysosomal enzyme alpha-galactosidase A (GLA), which results in the accumulation of globotriaosylceramide within the blood vessels and other tissues and organs. Symptoms associated with Fabry disease include pain from nerve damage and/or small vascular obstruction, renal insufficiency and eventual failure, cardiac complications such as high blood pressure and cardiomyopathy, dermatological symptoms such as formation of angiokeratomas, anhidrosis or hyperhidrosis, and ocular problems such as cornea verticillata, spoke-like cataract, and conjunctival and retinal vascular abnormalities. Treatments currently available include Genzyme's FABRAZYME® (agalsidase beta), which is a recombinant human alpha-galactosidase A produced in CHO cells and administered by intravenous infusion; Shire's REPLAGAL™ (agalsidase alfa), which is a recombinant human alpha-galactosidase A produced in human fibroblast cells and administered by intravenous infusion; and Amicus's GALAFOLD™

(migalastat or 1-deoxygalactonojirimycin) an orally administered small molecule chaperone that shifts the folding of abnormal alpha-galactosidase A to a functional conformation.

Nucleic Acid Constructs

[01188] In some embodiments, a CD40 inhibitor may inhibit an immune response elicited by a nucleic acid construct. In some embodiments, a nucleic acid construct comprises a coding sequence for a polypeptide of interest (e.g., an exogenous polypeptide coding sequence). In some embodiments, a nucleic acid construct described herein may comprises a polypeptide of interest coding sequence or a reverse complement of the polypeptide of interest coding sequence (e.g., an exogenous polypeptide coding sequence or a reverse complement of the exogenous polypeptide coding sequence).

[01189] The length of the nucleic acid constructs disclosed herein can vary. The construct can be, for example, from about 1 kb to about 5 kb, such as from about 1 kb to about 4.5 kb or about 1 kb to about 4 kb. An exemplary nucleic acid construct is between about 1 kb to about 5 kb in length or between about 1 kb to about 4 kb in length. Alternatively, a nucleic acid construct can be between about 1 kb to about 1.5 kb, about 1.5 kb to about 2 kb, about 2 kb to about 2.5 kb, about 2.5 kb to about 3 kb, about 3 kb to about 3.5 kb, about 3.5 kb to about 4 kb, about 4 kb to about 4.5 kb, or about 4.5 kb to about 5 kb in length. Alternatively, a nucleic acid construct can be, for example, no more than 5 kb, no more than 4.5 kb, no more than 4 kb, no more than 3.5 kb, no more than 3 kb, or no more than 2.5 kb in length.

[01190] The constructs can comprise deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), can be single-stranded, double-stranded, or partially single-stranded and partially double-stranded, and can be introduced into a host cell in linear or circular (e.g., minicircle) form. See, *e.g.*, US 2010/0047805, US 2011/0281361, and US 2011/0207221, each of which is herein incorporated by reference in their entirety for all purposes. If introduced in linear form, the ends of the construct can be protected (e.g., from exonucleolytic degradation) by known methods. For example, one or more dideoxynucleotide residues can be added to the 3′ terminus of a linear molecule and/or self-complementary oligonucleotides can be ligated to one or both ends. *See, e.g.*, Chang et al. (1987) *Proc. Natl. Acad. Sci. U.S.A.* 84:4959-4963 and Nehls et al. (1996) *Science* 272:886-889, each of which is herein incorporated by reference in their entirety for all purposes. Additional methods for protecting exogenous polynucleotides from degradation include, but are not limited to, addition of terminal amino group(s) and the use of modified internucleotide linkages such as, for example, phosphorothioates, phosphoramidates, and O-methyl ribose or deoxyribose residues. A construct can be introduced into a cell as part of a vector molecule having additional sequences such as, for example, replication origins,

promoters, and genes encoding antibiotic resistance. A construct may omit viral elements. Moreover, constructs can be introduced as a naked nucleic acid, can be introduced as a nucleic acid complexed with an agent such as a liposome or poloxamer, or can be delivered by viruses (e.g., adenovirus, adeno-associated virus (AAV), herpesvirus, retrovirus, or lentivirus).

[01191] The constructs disclosed herein can be modified on either or both ends to include one or more suitable structural features as needed and/or to confer one or more functional benefit. For example, structural modifications can vary depending on the method(s) used to deliver the constructs disclosed herein to a host cell (e.g., use of viral vector delivery or packaging into lipid nanoparticles for delivery). Such modifications include, for example, terminal structures such as inverted terminal repeats (ITR), hairpin, loops, and other structures such as toroids. For example, the constructs disclosed herein can comprise one, two, or three ITRs or can comprise no more than two ITRs. Various methods of structural modifications are known.

[01192] In some embodiments, a nucleic acid construct described herein may not comprise a promoter that drives the expression of the polypeptide of interest. in other cases the construct may comprise a promoter and/or enhancer, for example a constitutive promoter or an inducible or tissue-specific (e.g., liver- or platelet-specific) promoter that drives expression of the polypeptide of interest in an episome or upon integration. Non-limiting exemplary constitutive promoters include cytomegalovirus immediate early promoter (CMV), simian virus (SV40) promoter, adenovirus major late (MLP) promoter, Rous sarcoma virus (RSV) promoter, mouse mammary tumor virus (MMTV) promoter, phosphoglycerate kinase (PGK) promoter, elongation factor-alpha (EF1a) promoter, ubiquitin promoters, actin promoters, tubulin promoters, immunoglobulin promoters, a functional fragment thereof, or a combination of any of the foregoing. For example, the promoter may be a CMV promoter or a truncated CMV promoter. In another example, the promoter may be an EF1a promoter. Non-limiting exemplary inducible promoters include those inducible by heat shock, light, chemicals, peptides, metals, steroids, antibiotics, or alcohol. The inducible promoter may be one that has a low basal (non-induced) expression level, such as the Tet-On® promoter (Clontech). Although not required for expression, the constructs may comprise transcriptional or translational regulatory sequences such as promoters, enhancers, insulators, internal ribosome entry sites, additional sequences encoding peptides, and/or polyadenylation signals. The construct may comprise a sequence encoding a polypeptide of interest downstream of and operably linked to a signal sequence encoding a signal peptide

[01193] The constructs disclosed herein can be modified to include or exclude any suitable structural feature as needed for any particular use and/or that confers one or more desired

function.

[01194] The constructs disclosed herein can comprise a polyadenylation sequence or polyadenylation tail sequence (e.g., downstream or 3' of a polypeptide of interest coding sequence). Methods of designing a suitable polyadenylation tail sequence are well-known. The polyadenylation tail sequence can be encoded, for example, as a "poly-A" stretch downstream of the polypeptide of interest coding sequence. A poly-A tail can comprise, for example, at least 20, 30, 40, 50, 60, 70, 80, 90, or 100 adenines (SEQ ID NO: 1115), and optionally up to 300 adenines. In a specific example, the poly-A tail comprises 95, 96, 97, 98, 99, or 100 adenine nucleotides (SEQ ID NO: 1116). Methods of designing a suitable polyadenylation tail sequence and/or polyadenylation signal sequence are well known. For example, the polyadenylation signal sequence AAUAAA is commonly used in mammalian systems, although variants such as UAUAAA or AU/GUAAA have been identified. *See, e.g.*, Proudfoot (2011) *Genes & Dev.* 25(17):1770-82, herein incorporated by reference in its entirety for all purposes. The term polyadenylation signal sequence refers to any sequence that directs termination of transcription and addition of a poly-A tail to the mRNA transcript. In eukaryotes, transcription terminators are recognized by protein factors, and termination is followed by polyadenylation, a process of adding a poly(A) tail to the mRNA transcripts in presence of the poly(A) polymerase. The mammalian poly(A) signal typically consists of a core sequence, about 45 nucleotides long, that may be flanked by diverse auxiliary sequences that serve to enhance cleavage and polyadenylation efficiency. The core sequence consists of a highly conserved upstream element (AATAAA or AAUAAA) in the mRNA, referred to as a poly A recognition motif or poly A recognition sequence), recognized by cleavage and polyadenylation-specificity factor (CPSF), and a poorly defined downstream region (rich in Us or Gs and Us), bound by cleavage stimulation factor (CstF). Examples of transcription terminators that can be used include, for example, the human growth hormone (HGH) polyadenylation signal, the simian virus 40 (SV40) late polyadenylation signal, the rabbit beta-globin polyadenylation signal, the bovine growth hormone (BGH) polyadenylation signal, the phosphoglycerate kinase (PGK) polyadenylation signal, an AOX1 transcription termination sequence, a CYC1 transcription termination sequence, or any transcription termination sequence known to be suitable for regulating gene expression in eukaryotic cells. In one example, the polyadenylation signal is a simian virus 40 (SV40) late polyadenylation signal. In another example, the polyadenylation signal is a bovine growth hormone (BGH) polyadenylation signal or a CpG depleted BGH polyadenylation signal.

[01195] In some examples, the nucleic acid constructs disclosed herein can be bidirectional constructs. In some examples, the nucleic acid constructs disclosed herein can be unidirectional

constructs. Likewise, in some examples, the nucleic acid constructs disclosed herein can be in a vector (e.g., viral vector, such as AAV, or rAAV8) and/or a lipid nanoparticle.

Polypeptides of Interest

[01196] Any polypeptide of interest may be encoded by the nucleic acid constructs disclosed herein. In one example, the polypeptide of interest is a therapeutic polypeptide (e.g., a polypeptide that is lacking or deficient in a subject).

[01197] The polypeptide of interest can be a secreted polypeptide (e.g., a protein that is secreted by the cell and/or is functionally active as a soluble extracellular protein). Alternatively, the polypeptide of interest can be an intracellular polypeptide (e.g., a protein that is not secreted by the cell and is functionally active within the cell, including soluble cytosolic polypeptides).

[01198] The polypeptide of interest can be a wild type polypeptide. Alternatively, the polypeptide of interest can be a variant or mutant polypeptide.

[01199] In one example, the polypeptide of interest is a liver protein (e.g., a protein that is, endogenously produced in the liver and/or functionally active in the liver). In another example, the polypeptide of interest can be a circulating protein that is produced by the liver. In another example, the polypeptide of interest can be a non-liver protein.

[01200] In some embodiments, the polypeptide of interest is a multidomain therapeutic protein.

[01201] In some embodiments, the polypeptide of interest is a transgene product (e.g., a therapeutic polypeptide of interest or disclosed herein which is encoded by the transgene) disclosed herein.

[01202] In another example, the polypeptide of interest is an antigen-binding protein. An "antigen-binding protein" as disclosed herein includes any protein that binds to an antigen. Examples of antigen-binding proteins include an antibody, an antigen-binding fragment of an antibody, a multi-specific antibody (e.g., a bi-specific antibody), an scFv, a bis-scFv, a diabody, a triabody, a tetrabody, a V-NAR, a VHH, a VL, a F(ab), a F(ab)2, a DVD (dual variable domain antigen-binding protein), an SVD (single variable domain antigen-binding protein), a bispecific T-cell engager (BiTE), or a Davisbody (US Pat. No. 8,586,713, herein incorporated by reference herein in its entirety for all purposes).

[01203] An antigen-binding protein or antibody can be, for example, a neutralizing antigen-binding protein or antibody or a broadly neutralizing antigen-binding protein or antibody. A neutralizing antibody is an antibody that defends a cell from an antigen or infectious body by neutralizing any effect it has biologically. Broadly-neutralizing antibodies (bNAbs) affect multiple strains of a particular bacteria or virus. For example, broadly neutralizing antibodies can focus on conserved functional targets, attacking a vulnerable site on conserved bacterial or viral

proteins (e.g., a vulnerable site on the influenza viral protein hemagglutinin). Antibodies developed by the immune system upon infection or vaccination tend to focus on easily accessible loops on the bacterial or viral surface, which often have great sequence and conformational variability. This is a problem for two reasons: the bacteria or virus population can quickly evade these antibodies, and the antibodies are attacking portions of the protein that are not essential for function. Broadly neutralizing antibodies—termed "broadly" because they attack many strains of the bacteria or virus, and "neutralizing" because they attack key functional sites in the bacteria or virus and block infection—can overcome these problems. Unfortunately, however, these antibodies usually come too late and do not provide effective protection from the disease.

[01204] The antigen-binding proteins disclosed herein can target any antigen. The term "antigen" refers to a substance, whether an entire molecule or a domain within a molecule, which is capable of eliciting production of antibodies with binding specificity to that substance. The term antigen also includes substances, which in wild type host organisms would not elicit antibody production by virtue of self-recognition, but can elicit such a response in a host animal with appropriate genetic engineering to break immunological tolerance.

[01205] As one example, the targeted antigen can be a disease-associated antigen. The term "disease-associated antigen" refers to an antigen whose presence is correlated with the occurrence or progression of a particular disease. For example, the antigen can be in a disease-associated protein (i.e., a protein whose expression is correlated with the occurrence or progression of the disease). Optionally, a disease-associated protein can be a protein that is expressed in a particular type of disease but is not normally expressed in healthy adult tissue (i.e., a protein with disease-specific expression or disease-restricted expression). However, a disease-associated protein does not have to have disease-specific or disease-restricted expression.

[01206] As one example, a disease-associated antigen can be a cancer-associated antigen. The term "cancer-associated antigen" refers to an antigen whose presence is correlated with the occurrence or progression of one or more types of cancer. For example, the antigen can be in a cancer-associated protein (i.e., a protein whose expression is correlated with the occurrence or progression of one or more types of cancer). For example, a cancer-associated protein can be an oncogenic protein (i.e., a protein with activity that can contribute to cancer progression, such as proteins that regulate cell growth), or it can be a tumor-suppressor protein (i.e., a protein that typically acts to alleviate the potential for cancer formation, such as through negative regulation of the cell cycle or by promoting apoptosis). Optionally, a cancer-associated protein can be a

protein that is expressed in a particular type of cancer but is not normally expressed in healthy adult tissue (i.e., a protein with cancer-specific expression, cancer-restricted expression, tumor-specific expression, or tumor-restricted expression). However, a cancer-associated protein does not have to have cancer-specific, cancer-restricted, tumor-specific, or tumor-restricted expression. Examples of proteins that are considered cancer-specific or cancer-restricted are cancer testis antigens or oncofetal antigens. Cancer testis antigens (CTAs) are a large family of tumor-associated antigens expressed in human tumors of different histological origin but not in normal tissue, except for male germ cells. In cancer, these developmental antigens can be re-expressed and can serve as a locus of immune activation. Oncofetal antigens (OFAs) are proteins that are typically present only during fetal development but are found in adults with certain kinds of cancer.

[01207] As another example, a disease-associated antigen can be an infectious-disease-associated antigen. The term "infectious-disease-associated antigen" refers to an antigen whose presence is correlated with the occurrence or progression of a particular infectious disease. For example, the antigen can be in an infectious-disease-associated protein (i.e., a protein whose expression is correlated with the occurrence or progression of the infectious disease). Optionally, an infectious-disease-associated protein can be a protein that is expressed in a particular type of infectious disease but is not normally expressed in healthy adult tissue (i.e., a protein with infectious-disease-specific expression or infectious-disease-restricted expression). However, an infectious-disease-associated protein does not have to have infectious-disease-specific or infectious-disease-restricted expression. For example, the antigen can be a viral antigen or a bacterial antigen. Such antigens include, for example, molecular structures on the surface of viruses or bacteria (e.g., viral proteins or bacterial proteins) that are recognized by the immune system and are capable of triggering an immune response.

[01208] Examples of viral antigens include antigens within proteins expressed by the Zika virus or influenza (flu) viruses. Zika is a virus spread to people primarily through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. Albopictus*). Zika virus infection during pregnancy can cause microcephaly and other severe brain defects. For example, a Zika antigen can be, but is not limited to, an antigen within a Zika virus envelope (Env) protein. Influenza virus is a virus that causes an infectious disease called influenza (commonly known as "the flu"). Three types of influenza viruses affect people, called Type A, Type B, and Type C. An influenza antigen can be, but is not limited to, an antigen within the hemagglutinin protein. Viral antigens and bacterial antigens also include antigens on other viruses and other bacteria. Examples of

antibodies targeting influenza hemagglutinin are provided, e.g., in WO 2016/100807, herein incorporated by reference in its entirety for all purposes.

[01209] Examples of bacterial antigens include antigens within proteins expressed by *Pseudomonas aeruginosa* (e.g., an antigen within PcrV, which is a type III virulence system translocating protein). *Pseudomonas aeruginosa* is an opportunistic bacterial pathogen that causes fatal acute lung infections in critically ill individuals. Its pathogenesis is associated with bacterial virulence conferred by the type III secretion system (TTSS), through which *P. aeruginosa* causes necrosis of the lung epithelium and disseminates into the circulation, resulting in bacteremia, sepsis, and mortality. TTSS allows *P. aeruginosa* to directly translocate cytotoxins into eukaryotic cells, inducing cell death. The *P. aeruginosa* V-antigen PcrV, a homolog of the *Yersinia* V-antigen LcrV, is an indispensable contributor to TTS toxin translocation.

[01210] The antigen-binding protein can be a single-chain antigen-binding protein such as an scFv. Alternatively, the antigen-binding protein is not a single-chain antigen-binding protein. For example, the antigen-binding protein can include separate light and heavy chains. The heavy chain coding sequence can be upstream of the light chain coding sequence, or the light chain coding sequence can be upstream of the heavy chain coding sequence.

[01211] Signal sequences (i.e., N-terminal signal sequences) mediate targeting of nascent secretory and membrane proteins to the endoplasmic reticulum (ER) in a signal recognition particle (SRP)-dependent manner. Usually, signal sequences are cleaved off co-translationally so that signal peptides and mature proteins are generated. Examples of exogenous signal sequences or signal peptides that can be used include, for example, the signal sequence/peptide from mouse albumin, human albumin, mouse ROR1, human ROR1, human azurocidin, *Cricetulus griseus* Ig kappa chain V III region MOPC 63 like, and human Ig kappa chain V III region VG. Any other known signal sequence/peptide can also be used.

[01212] One or more of the nucleic acids in the antigen-binding-protein coding sequence (e.g., a heavy chain coding sequence and a light chain coding sequence) can be together in a multicistronic expression construct. For example, a nucleic acid encoding a heavy chain and a light chain can be together in a bicistronic expression construct. Multicistronic expression vectors simultaneously express two or more separate proteins from the same mRNA (i.e., a transcript produced from the same promoter). Suitable strategies for multicistronic expression of proteins include, for example, the use of a 2A peptide and the use of an internal ribosome entry site (IRES). As one example, such multicistronic vectors can use one or more internal ribosome entry sites (IRES) to allow for initiation of translation from an internal region of an mRNA. As

another example, such multicistronic vectors can use one or more 2A peptides. These peptides are small "self-cleaving" peptides, generally having a length of 18–22 amino acids and produce equimolar levels of multiple genes from the same mRNA. Ribosomes skip the synthesis of a glycyl-prolyl peptide bond at the C-terminus of a 2A peptide, leading to the "cleavage" between a 2A peptide and its immediate downstream peptide. *See, e.g.*, Kim et al. (2011) *PLoS One* 6(4): e18556, herein incorporated by reference in its entirety for all purposes. The "cleavage" occurs between the glycine and proline residues found on the C-terminus, meaning the upstream cistron will have a few additional residues added to the end, while the downstream cistron will start with the proline. As a result, the "cleaved-off" downstream peptide has proline at its N-terminus. 2A-mediated cleavage is a universal phenomenon in all eukaryotic cells. 2A peptides have been identified from picornaviruses, insect viruses and type C rotaviruses. *See, e.g.*, Szymczak et al. (2005) *Expert Opin Biol Ther* 5:627-638, herein incorporated by reference in its entirety for all purposes. Examples of 2A peptides that can be used include *Thosea asigna* virus 2A (T2A); porcine teschovirus-1 2A (P2A); equine rhinitis A virus (ERAV) 2A (E2A); and FMDV 2A (F2A). GSG residues can be added to the 5' end of any of these peptides to improve cleavage efficiency.

[01213] In some nucleic acid constructs, a nucleic acid encoding a furin cleavage site is included between the light chain coding sequence and the heavy chain coding sequence. In some nucleic acid construct, a nucleic acid encoding a linker (e.g., GSG) is included between the light chain coding sequence and the heavy chain coding sequence (e.g., directly upstream of the 2A peptide coding sequence). For example, a furin cleavage site can be included upstream of a 2A peptide, with both the furin cleavage site and the 2A peptide being located between the light chain and the heavy chain (i.e., upstream chain – furin cleavage site – 2A peptide – downstream chain). During translation, a first cleavage event will occur at the 2A peptide sequence. However, most of the 2A peptide will remain attached as a remnant to the C-terminus of the upstream chain (e.g., light chain if the light chain is upstream of the heavy chain, or heavy chain if the heavy chain is upstream of the light chain), with one amino acid added to the N-terminus of the downstream chain (or the N-terminus of a signal sequence, if a signal sequence is included upstream of the downstream chain). A second cleavage event, initiated at the furin cleavage site, yields the upstream chain without the 2A remnants in order to obtain a more native heavy chain or light chain by post-translational processing.

Lipid Nanoparticles

[01214] In some embodiments, a CD40 inhibitor may inhibit an immune response elicited by a lipid nanoparticle. As a non-limiting example, lipid nanoparticles can comprise a nucleic acid

construct encoding a polypeptide of interest disclosed herein (e.g., a transgene product including a therapeutic agent, e.g., a therapeutic polypeptide).

[01215] Lipid formulations can protect biological molecules from degradation while improving their cellular uptake. Lipid nanoparticles are particles comprising a plurality of lipid molecules physically associated with each other by intermolecular forces. These include microspheres (including unilamellar and multilamellar vesicles, e.g., liposomes), a dispersed phase in an emulsion, micelles, or an internal phase in a suspension. Such lipid nanoparticles can be used to encapsulate one or more nucleic acids or proteins for delivery. Formulations which contain cationic lipids are useful for delivering polyanions such as nucleic acids. Other lipids that can be included are neutral lipids (i.e., uncharged or zwitterionic lipids), anionic lipids, helper lipids that enhance transfection, and stealth lipids that increase the length of time for which nanoparticles can exist *in vivo*. Examples of suitable cationic lipids, neutral lipids, anionic lipids, helper lipids, and stealth lipids can be found in WO 2016/010840 A1 and WO 2017/173054 A1, each of which is herein incorporated by reference in its entirety for all purposes. An exemplary lipid nanoparticle can comprise a cationic lipid and one or more other components. In one example, the other component can comprise a helper lipid such as cholesterol. In another example, the other components can comprise a helper lipid such as cholesterol and a neutral lipid such as distearoylphosphatidylcholine or 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC). In another example, the other components can comprise a helper lipid such as cholesterol, an optional neutral lipid such as DSPC, and a stealth lipid such as S010, S024, S027, S031, or S033.

[01216] The LNP may contain one or more or all of the following: (i) a lipid for encapsulation and for endosomal escape; (ii) a neutral lipid for stabilization; (iii) a helper lipid for stabilization; and (iv) a stealth lipid. See, e.g., Finn et al. (2018) Cell Rep. 22(9):2227-2235 and WO 2017/173054 A1, each of which is herein incorporated by reference in its entirety for all purposes. In some LNPs, the lipid component comprises an amine lipid such as a biodegradable, ionizable lipid. In some instances, the lipid component comprises biodegradable, ionizable lipid, cholesterol, DSPC, and PEG-DMG.

[01217] In some examples, the LNPs comprise cationic lipids. In some examples, the LNPs comprise (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate) or another ionizable lipid. See, e.g., WO 2019/067992, WO 2017/173054, WO 2015/095340, and WO 2014/136086, each of which is herein incorporated by reference in its entirety for all purposes. In some examples, the LNPs comprise molar ratios of a

cationic lipid amine to RNA phosphate (N:P) of about 4.5, about 5.0, about 5.5, about 6.0, or about 6.5. In some examples, the terms cationic and ionizable in the context of LNP lipids are interchangeable (e.g., wherein ionizable lipids are cationic depending on the pH).

[01218] The lipid for encapsulation and endosomal escape can be a cationic lipid. The lipid can also be a biodegradable lipid, such as a biodegradable ionizable lipid. One example of a suitable lipid is Lipid A or LP01, which is (9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate, also called 3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,12Z)-octadeca-9,12-dienoate. See, e.g., Finn et al. (2018) Cell Rep. 22(9):2227-2235 and WO 2017/173054 A1, each of which is herein incorporated by reference in its entirety for all purposes. Another example of a suitable lipid is Lipid B, which is ((5-((dimethylamino)methyl)-1,3-phenylene)bis(oxy))bis(octane-8,1-diyl)bis(decanoate), also called ((5-((dimethylamino)methyl)-1,3-phenylene)bis(oxy))bis(octane-8,1-diyl)bis(decanoate). Another example of a suitable lipid is Lipid C, which is 2-((4-(((3-(dimethylamino)propoxy)carbonyl)oxy)hexadecanoyl)oxy)propane-1,3-diyl(9Z,9'Z,12Z,12'Z)-bis(octadeca-9,12-dienoate). Another example of a suitable lipid is Lipid D, which is 3-(((3-(dimethylamino)propoxy)carbonyl)oxy)-13-(octanoyloxy)tridecyl 3-octylundecanoate. Other suitable lipids include heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (also known as [(6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl] 4-(dimethylamino)butanoate or Dlin-MC3-DMA (MC3))).

[01219] Some such lipids suitable for use in the LNPs described herein are biodegradable *in vivo*.

[01220] Such lipids may be ionizable depending upon the pH of the medium they are in. For example, in a slightly acidic medium, the lipids may be protonated and thus bear a positive charge. Conversely, in a slightly basic medium, such as, for example, blood where pH is approximately 7.35, the lipids may not be protonated and thus bear no charge. In some embodiments, the lipids may be protonated at a pH of at least about 9, 9.5, or 10. The ability of such a lipid to bear a charge is related to its intrinsic pKa. For example, the lipid may, independently, have a pKa in the range of from about 5.8 to about 6.2.

[01221] Neutral lipids function to stabilize and improve processing of the LNPs. Examples of suitable neutral lipids include a variety of neutral, uncharged or zwitterionic lipids. Examples of neutral phospholipids suitable for use in the present disclosure include, but are not limited to, 5-heptadecylbenzene-1,3-diol (resorcinol), dipalmitoylphosphatidylcholine (DPPC), distearoylphosphatidylcholine or 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC),

phosphocholine (DOPC), dimyristoylphosphatidylcholine (DMPC), phosphatidylcholine (PLPC), 1,2-diarachidonoyl-sn-glycero-3-phosphocholine (DAPC), phosphatidylethanolamine (PE), egg phosphatidylcholine (EPC), dilauryloylphosphatidylcholine (DLPC), dimyristoylphosphatidylcholine (DMPC), 1-myristoyl-2-palmitoyl phosphatidylcholine (MPPC), 1-palmitoyl-2-myristoyl phosphatidylcholine (PMPC), 1-palmitoyl-2-stearoyl phosphatidylcholine (PSPC), 1,2-diarachidoyl-sn-glycero-3-phosphocholine (DBPC), 1-stearoyl-2-palmitoyl phosphatidylcholine (SPPC), 1,2-dieicosenoyl-sn-glycero-3-phosphocholine (DEPC), palmitoyloleoyl phosphatidylcholine (POPC), lysophosphatidyl choline, dioleoyl phosphatidylethanolamine (DOPE), dilinoleoylphosphatidylcholine distearoylphosphatidylethanolamine (DSPE), dimyristoyl phosphatidylethanolamine (DMPE), dipalmitoyl phosphatidylethanolamine (DPPE), palmitoyloleoyl phosphatidylethanolamine (POPE), lysophosphatidylethanolamine, 1-stearoyl-2-oleoyl-sn-glycero-3-phosphocholine (SOPC), and combinations thereof. For example, the neutral phospholipid may be selected from the group consisting of distearoylphosphatidylcholine (DSPC) and dimyristoyl phosphatidyl ethanolamine (DMPE).

[01222] Helper lipids include lipids that enhance transfection. The mechanism by which the helper lipid enhances transfection can include enhancing particle stability. In certain cases, the helper lipid can enhance membrane fusogenicity. Helper lipids include steroids, sterols, and alkyl resorcinols. Examples of suitable helper lipids suitable include cholesterol, 5-heptadecylresorcinol, and cholesterol hemisuccinate. In one example, the helper lipid may be cholesterol or cholesterol hemisuccinate.

[01223] Stealth lipids include lipids that alter the length of time the nanoparticles can exist *in vivo*. Stealth lipids may assist in the formulation process by, for example, reducing particle aggregation and controlling particle size. Stealth lipids may modulate pharmacokinetic properties of the LNP. Suitable stealth lipids include lipids having a hydrophilic head group linked to a lipid moiety.

[01224] The hydrophilic head group of stealth lipid can comprise, for example, a polymer moiety selected from polymers based on PEG (sometimes referred to as poly(ethylene oxide)), poly(oxazoline), poly(vinyl alcohol), poly(glycerol), poly(N- vinylpyrrolidone), polyaminoacids, and poly N-(2-hydroxypropyl)methacrylamide. The term PEG means any polyethylene glycol or other polyalkylene ether polymer. In certain LNP formulations, the PEG, is a PEG-2K, also termed PEG 2000, which has an average molecular weight of about 2,000 daltons. See, e.g., WO 2017/173054 A1, herein incorporated by reference in its entirety for all purposes.

[01225] The lipid moiety of the stealth lipid may be derived, for example, from diacylglycerol or diacylglycamide, including those comprising a dialkylglycerol or dialkylglycamide group having alkyl chain length independently comprising from about C4 to about C40 saturated or unsaturated carbon atoms, wherein the chain may comprise one or more functional groups such as, for example, an amide or ester. The dialkylglycerol or dialkylglycamide group can further comprise one or more substituted alkyl groups.

[01226] As one example, the stealth lipid may be selected from PEG-dilauroylglycerol, PEG-dimyristoylglycerol (PEG-DMG), PEG-dipalmitoylglycerol, PEG-distearoylglycerol (PEG- DSPE), PEG-dilaurylglycamide, PEG- dimyristylglycamide, PEG-dipalmitoylglycamide, and PEG-distearoylglycamide, PEG- cholesterol (l-[8'-(Cholest-5-en-3[beta]-oxy)carboxamido-3',6'-dioxaoctanyl]carbamoyl-[omega]-methyl-poly(ethylene glycol), PEG-DMB (3,4-ditetradecoxylbenzyl-[omega]-methyl-poly(ethylene glycol)ether), 1,2-dimyristoyl-sn- glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (PEG2k- DMPE),or 1,2-dimyristoyl-rac-glycero-3-methylpolyoxyethylene glycol-2000 (PEG2k-DMG), 1,2- distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (PEG2k-DSPE), 1,2-distearoyl-sn-glycerol, methoxypoly ethylene glycol (PEG2k-DSG), poly(ethylene glycol)-2000-dimethacrylate (PEG2k-DMA), and 1,2- distearyloxypropyl-3-amine-N-[methoxy(polyethylene glycol)-2000] (PEG2k-DSA). In one particular example, the stealth lipid may be PEG2k-DMG.

[01227] In some embodiments, the PEG lipid includes a glycerol group. In some embodiments, the PEG lipid includes a dimyristoylglycerol (DMG) group. In some embodiments, the PEG lipid comprises PEG2k. In some embodiments, the PEG lipid is a PEG-DMG. In some embodiments, the PEG lipid is a PEG2k-DMG. In some embodiments, the PEG lipid is 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000. In some embodiments, the PEG2k-DMG is 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000.

[01228] The LNPs can comprise different respective molar ratios of the component lipids in the formulation. The mol-% of the CCD lipid may be, for example, from about 30 mol-% to about 60 mol-%, from about 35 mol-% to about 55 mol-%, from about 40 mol-% to about 50 mol-%, from about 42 mol-% to about 47 mol-%, or about 45%. The mol-% of the helper lipid may be, for example, from about 30 mol-% to about 60 mol-%, from about 35 mol-% to about 55 mol-%, from about 40 mol-% to about 50 mol-%, from about 41 mol-% to about 46 mol-%, or about 44 mol-%. The mol-% of the neutral lipid may be, for example, from about 1 mol-% to about 20 mol-%, from about 5 mol-% to about 15 mol-%, from about 7 mol-% to about 12 mol-%, or about 9 mol-%. The mol-% of the stealth lipid may be, for example, from about 1 mol-% to about 10 mol-

%, from about 1 mol-% to about 5 mol-%, from about 1 mol-% to about 3 mol-%, about 2 mol-%, or about 1 mol-%.

[01229] The LNPs can have different ratios between the positively charged amine groups of the biodegradable lipid (N) and the negatively charged phosphate groups (P) of the nucleic acid to be encapsulated. This may be mathematically represented by the equation N/P. For example, the N/P ratio may be from about 0.5 to about 100, from about 1 to about 50, from about 1 to about 25, from about 1 to about 10, from about 1 to about 7, from about 3 to about 5, from about 4 to about 5, about 4, about 4.5, or about 5. The N/P ratio can also be from about 4 to about 7 or from about 4.5 to about 6. In specific examples, the N/P ratio can be 4.5 or can be 6.

[01230] Exemplary dosing of LNPs includes about 0.1, about 0.25, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 8, or about 10 mg/kg body weight (mpk) or about 0.1 to about 10, about 0.25 to about 10, about 0.3 to about 10, about 0.5 to about 10, about 1 to about 10, about 2 to about 10, about 3 to about 10, about 4 to about 10, about 5 to about 10, about 6 to about 10, about 8 to about 10, about 0.1 to about 8, about 0.1 to about 6, about 0.1 to about 5, about 0.1 to about 4, about 0.1 to about 3, about 0.1 to about 2, about 0.1 to about 1, about 0.1 to about 0.5, about 0.1 to about 0.3, about 0.1 to about 0.25, about 0.25 to about 8, about 0.3 to about 6, about 0.5 to about 5, about 1 to about 5, or about 2 to about 3 mg/kg body weight with respect to total cargo content. Such LNPs can be administered, for example, intravenously. In one example, LNP doses between about 0.01 mg/kg and about 10 mg/kg, between about 0.1 and about 10 mg/kg, or between about 0.01 and about 0.3 mg/kg can be used. For example, LNP doses of about 0.01, about 0.03, about 0.1, about 0.3, about 1, about 3, or about 10 mg/kg can be used. Additional exemplary dosing of LNPs includes about 0.1, about 0.25, about 0.3, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 8, or about 10 mg/kg (mpk) body weight or about 0.1 to about 10, about 0.25 to about 10, about 0.3 to about 10, about 0.5 to about 10, about 1 to about 10, about 2 to about 10, about 3 to about 10, about 4 to about 10, about 5 to about 10, about 6 to about 10, about 8 to about 10, about 0.1 to about 8, about 0.1 to about 6, about 0.1 to about 5, about 0.1 to about 4, about 0.1 to about 3, about 0.1 to about 2, about 0.1 to about 1, about 0.1 to about 0.5, about 0.1 to about 0.3, about 0.1 to about 0.25, about 0.25 to about 8, about 0.3 to about 6, about 0.5 to about 5, about 1 to about 5, or about 2 to about 3 mg/kg body weight with respect to total cargo content. Such LNPs can be administered, for example, intravenously. In one example, LNP doses between about 0.01 mg/kg and about 10 mg/kg, between about 0.1 and about 10 mg/kg, or between about 0.01 and about 0.3 mg/kg can be used. For example, LNP doses of about 0.01, about 0.03, about 0.1, about 0.3, about 0.5, about 1, about 2, about 3, or about 10 mg/kg can be

used. In another example, LNP doses between about 0.5 and about 10, between about 0.5 and about 5, between about 0.5 and about 3, between about 1 and about 10, between about 1 and about 5, between about 1 and about 3, or between about 1 and about 2 mg/kg can be used. In another example, LNP doses between about 0.5 and about 3, between about 0.5 and about 2.5, between about 0.5 and about 2, between about 0.5 and about 1.5, between about 0.5 and about 1, between about 1 and about 3, between about 1 and about 2.5, between about 1 and about 2, or between about 1 and about 1.5 mg/kg can be used. In another example, an LNP dose of about 1 mg/kg can be used.

[01231] Other examples of suitable LNPs can be found, e.g., in WO 2019/067992, WO 2020/082042, US 2020/0270617, WO 2020/082041, US 2020/0268906, WO 2020/082046 (see, e.g., pp. 85-86), and US 2020/0289628, each of which is herein incorporated by reference in its entirety for all purposes.

CD40 inhibitors

[01232] A CD40 inhibitor suitable for use in accordance with any of the above-described methods can comprise, without limitation, any of various CD40 antigen-binding molecules described herein, for example, anti-CD40 antibodies, or functional fragments thereof, including monospecific anti-CD40 antibodies, bispecific anti-CD40 antibodies, or multispecific anti-CD40 antibodies, or functional fragments thereof. In some embodiments, a CD40 inhibitor can comprise an CD40 antigen-binding molecule as disclosed herein (e.g., a CD40xCD40 bispecific antigen-binding molecule, e.g., as disclosed in any one of **Tables 3-6**).

[01233] In some embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof. The anti-CD40 antibody may comprise any anti-CD40 antibody known in the art. Non-limiting examples of anti-CD40 antibodies include CD40 Monoclonal Antibody (1C10) (eBioscience™), CD40 Monoclonal Antibody (HM40-3) (eBioscience™), CD40 Monoclonal Antibody (5C3) (eBioscience™), CD40 Monoclonal Antibody (9G10) (Invitrogen), CD40 Monoclonal Antibody (3/23) (Invitrogen), CD40 Monoclonal Antibody (HB14) (Invitrogen), CD40 Polyclonal Antibody (Invitrogen), CD40 Monoclonal Antibody (OTI1F12), TrueMAB™ (OriGene), CD40 Recombinant Rabbit Monoclonal Antibody (5V8X7) (Invitrogen), CD40 Monoclonal Antibody (LOB7/6) (Invitrogen), CD40 Monoclonal Antibody (5C3) (Invitrogen), CD40 Monoclonal Antibody (HI40a) (Invitrogen), CD40 Monoclonal Antibody (IL-A156) (Invitrogen), CD40 Monoclonal Antibody (C7) (Invitrogen), CD40 Polyclonal Antibody (Invitrogen, e.g., Cat # PA5-111025, Cat #PA5-111024, Cat #PA5-109301, Cat #PA5-117850, Cat #PA5-27419, Cat #PA5-78980, Cat #PA1-31075), CD40 Monoclonal Antibody (3/23) (Invitrogen), CD40

Monoclonal Antibody (HB14) (Invitrogen), CD40 Recombinant Rabbit Monoclonal Antibody (Bethyl Laboratories), CD40 Monoclonal Antibody (OTI8B8), TrueMAB™ (OriGene), CD40 Monoclonal Antibody (OTI1F12), TrueMAB™ (OriGene), CD40 Monoclonal Antibody (OTI5C9), TrueMAB™ (OriGene), CD40 Monoclonal Antibody (UMAB255), UltraMAB™ (OriGene), CD40 Monoclonal Antibody (2A8G5) (Proteintech), CD40 Monoclonal Antibody (G28.5) (Proteintech), CD40 Monoclonal Antibody (1C10) (Proteintech), CD40 Monoclonal Antibody (G28.5) (Proteintech), CD40 Monoclonal Antibody (2A8G5) (Proteintech), CD40 Monoclonal Antibody (UMAB183), UltraMAB™ (OriGene), CD40 Monoclonal Antibody (UMAB183), UltraMAB™ (OriGene), CD40 Monoclonal Antibody (HB14) (AbboMax), CD40 Monoclonal Antibody (1G1) (Abnova), CD40 Polyclonal Antibody (AbboMax, Cat #500-3704), CD40 Monoclonal Antibody (FGK45) (Leinco Technologies), CD40 Monoclonal Antibody (3D9) (Abnova), and CD40 Monoclonal Antibody (2H8) (Abnova).

[01234] In some embodiments, the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof. The antagonistic anti-CD40 antibody may comprise any antagonistic anti-CD40 antibody known in the art. Non-limiting examples of antagonistic anti-CD40 antibodies include iscalimab (also known as CFZ533) disclosed in Kahaly et al. (2019) J. Endocr. Sco. 3:doi.org/10.1210/js.2019-0R19-6, Fisher et al. (2017) Arthritis Rheumatol. 69:1784, Farkash et al. (2019) Am. J. Transplant. 19:632, U.S. Pat. No. US 8,828,396, International Patent Application Publication No. WO 2012/075111, and clinical trial NCT02291029 sponsored by Novartis Pharmaceuticals; ravagalimab (also known as ABBV-323 and Ab102) disclosed in International Patent Application Publication No. WO 2016/196314 and U.S. Patent Application Publication No. US 2022/0289858; BI-655064 disclosed in Visvannathan et al. (2016) Arthritis Rheumatol. 68:1588, U.S. Pat. No. 8,591,900, and clinical trial NCT03385564 sponsored by Boehringer Ingelheim; bleselumab (also known as ASKP1240 or 341G2) disclosed in Anil et al. (2018) Biopharm. Drug Dispos. 39:245-255, Harland et al. (2017) Am. J. Transplant. 17:159-171, U.S. Pat. Nos. 8,716,451 and 8,568,725, and clinical trials NCT01585233 and NCT02921789 sponsored by Astellas Pharma; ch5D12 disclosed in Kasran et al. (2005) Aliment. Pharmacol. Ther. 22:111-122 and U.S. Patent Application Publication No. US 2008/0085531; lucatumumab (also known as HCD122 or CHIR-12.12) disclosed in Bensinger et al. (2012) British J. Haematology 159:58-66, Byrd et al. (2012) Leuk. Lymphoma 53:10.3109/10428194.2012.681655, International Patent Application Publication No. WO 2005/044854, U.S. Patent Application Publication No. US 2007/0110754 and U.S. Pat. No. US 8,828,396; CHIR-5.9 disclosed in International Patent Application Publication No. WO 2005/044854 and U.S. Pat. No. 8,637,032; abiprubart [KPL-404] disclosed in clinical trial

NCT04497662 sponsored by Kiniksa Pharmaceuticals, Ltd. as well as in U.S. Patent Application Publication Nos. US 2023/0287132, US 2023/0203179, US 2023/0183367, and US 2023/0279135; BIIB063 disclosed in Musselli et al. (2017) 2017 ACR/ARHP Annual Meeting Abstract and International Patent Application Publication No. WO 2016028810; V19 and V15 disclosed in U.S. Patent Application Publication No. US 2022/0135694; h2C10 and variants thereof disclosed in U.S. Pat. No. 11,439,706; FFP104 (also known as PG102) disclosed in U.S. Pat. Nos. 8,669,352 and 11,396,552, International Patent Application Publication No. WO 2001/024823, U.S. Patent Application Publication No. US 2008/0085531, Bankert et al. (2015) J. Immunol. 194:4319-4327, and clinical trials NCT02193360 and NCT02465944 sponsored by Fast Forward Pharmaceuticals; Ab101 disclosed in U.S. Patent Application Publication No. US 2022/0289858; Antibody A, antibody B, Antibody C, disclosed in U.S. Pat. No. 11,242,394; G28.5 disclosed in International Patent Application Publication No. WO 2016028810; BMS3h-37, BMS3h-38, BMS3h-56, and BMS3h-198 disclosed in International Patent Application Publication No. WO2012145673A1,and Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3], and Y12XX-hz42 [Vh-hzl4;Vk-hz3] disclosed in International Patent Application Publication No. WO2020/106620A1, the contents of each of which are herein incorporated by reference in their entirety. An additional CD40 antibody useful in certain embodiments of the methods and compositions provided herein is teneliximab. Additional CD40 antagonist antibodies useful in certain embodiments of the methods and compositions provided herein are disclosed in, for example, International Patent Application Publication Nos. WO 02/11763, WO 02/28481, WO 03/045978, WO 03/029296, WO 03/028809, WO 2005/044854, WO 2006/073443, WO 2007/124299, WO 2011/123489, WO 2016/196,314, WO 2017/040566, WO 2017/060242, WO 2018/217976, WO2019/156565, WO 2020/144605, WO 2020/106620, WO 2020/006347, U.S. Patent Application Publication Nos. US 2020/0291123, US 2017/0158771, US 2008/0057070, and U.S. Pat. Nos. 5,874,082, 7,063,845, 9,125,893, 8,669,352, 9,598,494, 11,254,750, 11,780,927, 11,220,550, 11,202,827, 10,111,958, 11,242,397, 8,591,900, 9,475,879, 10,174,121, the contents of each of which are herein incorporated by reference in their entirety.

[01235] In some embodiments, a CD40 inhibitor may comprise daclizumab.

[01236] In some embodiments, a CD40 inhibitor may comprise, e.g., another CD40-CD40L inhibitor (e.g., an anti-CD40 antibody such as iscalimab [CFZ-533], ravagalimab [ABBV-323] /Ab102, BI-655064, bleselumab [ASKP1240], , ch5D12, lucatumumab [HCD122 or CHIR12.12], CHIR-5.9, abiprubart [KPL-404] PG102/FFP104, BIIB063, BMS3h-38, BMS3h-56, BMS3h-198, V19, V15, h2C10 and variants thereof , Ab101, Antibody A , Antibody B , Antibody C, G28.5,

Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3], Y12XX-hz42 [Vh-hzl4;Vk-hz3] or teneliximab; or an anti-CD40L antibody or antigen-binding protein such as dapirolizumab pegol, dazodalibep [VIB4920], frexalimab [INX-021], letolizumab [BMS-986004], MR-1, ruplizumab [BG9588], tegoprubart [AT-1501], and/or toralizumab [IDEC-131].

[01237] In some embodiments, the CD40 inhibitor may comprise a peptide such as but not limited to $KGYY_{15}$ (see, e.g., Vaitaitis et al., A CD40-targeted peptide controls and reverses type 1 diabetes in NOD mice Diabetologia. 2014 Nov;57(11):2366-73, herein incorporated by reference in its entirety for all purposes), $KGYY_6$ (Vaitaitis et al., A CD40 targeting peptide prevents severe symptoms in Experimental Autoimmune Encephalomyelitis J Neuroimmunol. 2019 Jul 15; 332: 8–15, herein incorporated by reference in its entirety for all purposes) and CD40–CD40L blocking cyclic heptapetide (CLPTRHMAC (SEQ ID NO: 1109)).

[01238] In some embodiments, the CD40 inhibitor may comprise a small molecule inhibitor (e.g., DRI-C21045, BIO8898). In some embodiments, a small-molecule CD40 inhibitor may comprise any small-molecule as described, for example, in J. Chen, et al. Small-Molecule Inhibitors of the CD40-CD40L Costimulatory Protein-Protein Interaction J. Med. Chem., 60 (21) (2017), pp. 8906-8922; L.F. Silvian, et al. Small molecule inhibition of the TNF family cytokine CD40 ligand through a subunit fracture mechanism ACS Chem. Biol., 6 (6) (2011), pp. 636-647; G.M. Vaitaitis, et al.; E. Margolles-Clark, et al. Suramin inhibits the CD40-CD154 costimulatory interaction: a possible mechanism for immunosuppressive effects Biochem. Pharmacol., 77 (7) (2009), pp. 1236-1245; each of which is herein incorporated by reference in its entirety for all purposes.

[01239] The CD40 inhibitor can be used for inhibiting CD40L-induced activation of CD40, e.g., in or on a cell that expresses CD40 (e.g., a B cell, dendritic cell, monocyte, platelet, or macrophage). The CD40 inhibitor are able to suppress host B cell responses to new antigens. In AAV gene therapies, seronegative/naive subjects are dosed with AAV and develop antibody responses to the AAV capsid antigen. This antibody response prevents future re-dosing of AAV because the antibodies are neutralizing, and the antibody response is sustained for 10+ years. When AAV is co-administered with a CD40 inhibitor, the B cell response is suppressed and anti-AAV IgG and/or IgM responses are significantly suppressed. When a CD40 inhibitor is given during the period of AAV antigen exposure, the anti-AAV antibody response can be suppressed in animals. This allows re-dosing of any AAV gene therapy product.

[01240] In some embodiments, the CD40 inhibitor can prevent antibody formation against an immunogenic delivery vehicle described herein. As a non-limiting example, the CD40 inhibitor can prevent antibody formation against an AAV or portion thereof. The CD40 inhibitor can also

prevent antibody formation against certain LNP components (e.g., anti-PEG IgG), which can improve efficacy of LNP redosing. The CD40 inhibitor can also prevent antibody formation against, e.g., a transgene product described herein.

[01241] In some embodiments, the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof. In some embodiments, the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, and both antigen-binding domains bind to CD40.

[01242] In some embodiments, the anti-CD40xCD40 bispecific antibody comprises:

(a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

(b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

[01243] In some embodiments, D1 and D2 do not compete with one another for binding to human CD40.

[01244] In some embodiments, the anti-CD40xCD40 bispecific antibody:

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life of ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmin resonance at 25°C

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

[01245] In some embodiments, the anti-CD40xCD40 bispecific antibody inhibits CD40L-induced activation. In some embodiments, the anti-CD40xCD40 bispecific antibody inhibits CD40L-induced activation and does not significantly agonize CD40 in the absence of CD40L.

[01246] In some embodiments, the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8;

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28; and

(c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38.

[01247] In some embodiments, the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16.

[01248] In some embodiments, the D1 domain comprises:

(a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; or

(b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[01249] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[01250] In some embodiments, the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

[01251] In some embodiments, the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid

sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[01252] In some embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22.

[01253] In some embodiments, the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10.

[01254] In some embodiments, the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[01255] In some embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32.

[01256] In some embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[01257] In some embodiments, the anti-CD40xCD40 bispecific antibody comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[01258] In some embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[01259] In certain embodiments, the anti-CD40xCD40 bispecific antibody comprises a D1 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the

amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In certain embodiments, the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32. In certain embodiments, the D1 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[01260] In certain embodiments, the anti-CD40xCD40 bispecific antibody comprises a D2 domain that comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In certain embodiments, the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

[01261] In certain embodiments, the anti-CD40xCD40 bispecific antibody comprises:

a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and

a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

[01262] In certain embodiments, the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 and an LCVR comprising the amino acid sequence of SEQ ID NO: 10.

Dosage and Administration Regimens

[01263] In some embodiments, an amount of a CD40 antigen-binding molecule, e.g., a CD40 antigen-binding molecule (e.g., an anti-CD40xCD40 bispecific antibody), a CD40 inhibitor,

and/or an immunogen (e.g., an immunogenic delivery vehicle), or pharmaceutical composition thereof which is administered to a subject according to the methods disclosed herein is a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount that produces the desired effect for which it is administered. The subject can be from any suitable species, such as eukaryotic or mammalian subjects (e.g., non-human mammalian subject or human subject). A mammal can be, for example, a non-human mammal, a human, a rodent, a rat, a mouse, or a hamster. Other non-human mammals include, for example, non-human primates, e.g., monkeys (e.g., cynomolgus macaques) and apes. The term “non-human” excludes humans. Specific examples include, but are not limited to, humans, rodents, mice, rats, and non-human primates. In a specific example, the subject is a human. The human may be a patient. Likewise, cells can be any suitable type of cell. In a specific example, the cell or cells are a liver cell or liver cells such as a hepatocyte or hepatocytes (e.g., human liver cell(s) or human hepatocyte(s)).In some embodiments, the CD40 antigen-binding molecule (e.g., an anti-CD40xCD40 bispecific antibody), the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle), or pharmaceutical composition thereof, is administered to a subject as a weight-based dose. A "weight-based dose" *(e.g.,* a dose in mg/kg) is a dose of the CD40 antigen-binding molecule, the CD40 inhibitor and/or the immunogenic delivery vehicle that will change depending on the subject's weight.

[01264] In other embodiments, the CD40 antigen-binding molecule (e.g., an anti-CD40xCD40 bispecific antibody), the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle), is administered as a fixed dose. A "fixed dose" (e.g., a dose in mg) means that one dose of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle), is used for all subjects regardless of any specific subject-related factors, such as weight. In one particular embodiment, a fixed dose of an CD40 antigen-binding molecule, a CD40 inhibitor, and/or an immunogen is based on a predetermined weight or age.

[01265] Typically, a suitable dose of the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen can be in the range of about 0.001 to about 200.0 milligram per kilogram body weight of the recipient, generally in the range of about 1 to 50 mg per kilogram body weight. For example, the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen can be administered at about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, or about 50 mg/kg per single dose. Values and ranges intermediate to the recited values are also intended to be part of this disclosure. In some embodiments, the CD40 antigen-binding molecule and/or

the CD40 inhibitor and/or the immunogen is administered at about 20 mg/kg per single dose. In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen is administered at about 50 mg/kg per single dose.

[01266] In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen is administered as a fixed dose of between about 5 mg to about 2500 mg. In some embodiments, the antigen-binding molecule is administered as a fixed dose of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1500 mg, about 2000 mg, or about 2500 mg. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[01267] In some embodiments, the CD40 antigen-binding molecule (e.g., an anti-CD40xCD40 bispecific antibody) and/or the CD40 inhibitor and/or the immunogen (e.g., an immunogenic delivery vehicle) is administered to a subject at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen is administered to a subject about once every two weeks. In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen is administered to a subject about once a week. In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen is administered at about 20 mg/kg per single dose to a subject about once every two weeks. In some embodiments, the immunogenic delivery vehicle can be administered at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle) can be administered at a dosing frequency of about four times a year, twice a year, once a week, once every two years, once every three years, once every four years, once every five years, once every six years,

once every eight years, once every twelve years, or less frequently so long as a therapeutic response is achieved.

[01268] Dose ranges and frequency of administration of an immunogen, e.g., an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein can vary depending on the nature of, and/or the medical condition, as well as parameters of a specific subject and the route of administration used. As a non-limiting example, vector compositions can be administered to a subject at a dose ranging from about 1×10^5 plaque forming units (pfu) to about 1×10^{15} pfu, depending on mode of administration, the route of administration, the nature of the disease and condition of the subject. In some cases, the vector compositions can be administered at a dose ranging from about 1×10^8 pfu to about 1×10^{15} pfu, or from about 1×10^{10} pfu to about 1×10^{15} pfu, or from about 1×10^8 pfu to about 1×10^{12} pfu. A more accurate dose can also depend on the subject in which it is being administered. For example, a lower dose may be required if the subject is juvenile, and a higher dose may be required if the subject is an adult human subject. In certain embodiments, a more accurate dose can depend on the weight of the subject. In certain embodiments, for example, a juvenile human subject can receive from about 1×10^8 pfu to about 1×10^{10} pfu, while an adult human subject can receive a dose from about 1×10^{10} pfu to about 1×10^{12} pfu.

[01269] In some embodiments, an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein can be administered at a dose such as, but not limited to, 10^{12}, 10^{13}, 10^{14}, 10^{15}, and 10^{16} vector genomes/mL. Further exemplary vector doses include about 10^{12}, about 10^{13}, about 10^{14}, about 10^{15}, and about 10^{16} vector genomes (vg)/mL, or between about 10^{12} to about 10^{16}, between about 10^{12} to about 10^{15}, between about 10^{12} to about 10^{14}, between about 10^{12} to about 10^{13}, between about 10^{13} to about 10^{16}, between about 10^{14} to about 10^{16}, between about 10^{15} to about 10^{16}, or between about 10^{13} to about 10^{15} vg/mL. Other exemplary vector doses include about 10^{12}, about 10^{13}, about 10^{14}, about 10^{15}, and about 10^{16} vector genomes (vg)/kg of body weight, or between about 10^{12} to about 10^{16}, between about 10^{12} to about 10^{15}, between about 10^{12} to about 10^{14}, between about 10^{12} to about 10^{13}, between about 10^{13} to about 10^{16}, between about 10^{14} to about 10^{16}, between about 10^{15} to about 10^{16}, or between about 10^{13} to about 10^{15} vg/kg of body weight. In one example, the viral dose is between about 10^{13} to about 10^{14} vg/mL or vg/kg. In another example, the viral dose is between about 10^{12} to about 10^{13} vg/mL or vg/kg (e.g., between about 10^{12} to about 10^{13} vg/kg). In another example, the viral dose is between about 10^{12} to about 10^{14} vg/mL or vg/kg (e.g., between about 10^{12} to about 10^{14} vg/kg). For example, the viral dose can be between about 1.5E12 to about 1.5E13 vg/kg, can be about 1.5E12 vg/kg, or can be about 1.5E13 vg/kg.

In another example, the viral dose is about 2E13 vg/mL or vg/kg. In another example, the viral dose is about 1E12 to about 2E14 vg/kg.

[01270] In some embodiments, an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein can be administered at a dose of between about 3E11 vg/kg to about 5E13 vg/kg. In some embodiments, an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein can be administered at a dose of about 1E13 vg/kg.

[01271] In some embodiments, a subsequent dose of an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein may be higher than a first dose of an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein. In some embodiments, relatively low levels of transduction may be observed for an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein at a lower dose relative to a higher dose. In some embodiments, a higher dose relative to a lower dose of an immunogenic delivery vehicle such as a vector (e.g., a viral vector such as an AAV vector) described herein may be used to achieve higher levels of transduction.

[01272] In some embodiments, multiple doses of a CD40 antigen-binding molecule (e.g., an anti-CD40xCD40 bispecific antibody), a CD40 inhibitor, and/or an immunogen (e.g., an immunogenic delivery vehicle) are administered to a subject over a defined time course. In some embodiments, the methods of the present disclosure comprise sequentially administering to a subject multiple doses of the CD40 antigen-binding molecule, the CD40 inhibitor and/or the immunogen (e.g., an immunogenic delivery vehicle).

[01273] In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle such as a vector e.g. an AAV vector) may be administered in accordance with a repeat dosing regimen wherein the immunogen (e.g., an immunogenic delivery vehicle) may be administered a first time (e.g., in an initial dose) and then re-administered any number of subsequent times thereafter at any amount over the time course of treatment of a subject. For example, the immunogen may be re-administered once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more, over the time course of the treatment of a subject which can occur over any number of days, weeks, or years. In some embodiments, when the immunogen (e.g., an immunogenic delivery vehicle) comprises a vector, e.g., a viral vector such as an AAV vector, the vector which is administered first in a repeat dosing regimen may comprise the same vector which is re-administered second in the repeat dosing regimen, or any number of subsequent times thereafter. In some embodiments, when the immunogen

(e.g., an immunogenic delivery vehicle) comprises a vector, e.g., a viral vector such as an AAV vector, the vector which is administered first in a repeat dosing regimen may comprise a different vector than is re-administered second in the repeat dosing regimen, or any number of subsequent times thereafter.

[01274] In some embodiments, an immunogen (e.g., an immunogenic delivery vehicle), e.g., a viral vector such as an AAV vector, may be administered in accordance with a stepwise dosing regimen. Stepwise dosing of an immunogen can refer to breaking up (i.e., dividing) dosing of the same immunogen over multiple administrations. In some embodiments, the dosing of the same immunogen is broken up once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more, over the time course of the treatment of a subject which can occur over any number of days, weeks, or years. In some embodiments, when a stepwise dose regimen is used in the administration of an immunogen, e.g., an immunogenic delivery vehicle, e.g., a viral vector such as an AAV vector, the stepwise dosing regimen may result in a gradual increase in therapeutic transgene levels with each administration of the immunogen. Without wishing to be bound by theory, a stepwise dosing regimen used in the administration of an immunogen comprising an immunogenic delivery vehicle, e.g., a viral vector such as an AAV vector, can result in enhanced control over transgene expression in a cell and/or subject, since for some transgenes too much expression can result in its own pathology.

[01275] In some embodiments, an immunogen (e.g., an immunogenic delivery vehicle) is administered to a subject in combination with a CD40 antigen-binding molecule and/or a CD40 inhibitor. The CD40 antigen-binding molecule and/or the CD40 inhibitor can be administered prior to, simultaneously with, or after the immunogen. In one example, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered prior to the immunogen. In another example, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered prior to and after the immunogen. In another example, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered simultaneously with the immunogen. In some embodiments, when an immunogen (e.g., an immunogenic delivery vehicle) is administered to a subject in combination with a CD40 antigen-binding molecule and/or a CD40 inhibitor described herein, the CD40 antigen-binding molecule and/or a CD40 inhibitor allows for redosing of the immunogen, e.g., permitting stepwise dosing of the immunogen with lower doses (e.g., stepwise dosing of 2-3 doses of the immunogen with each dose being 2-3X lower than a dose would be in a one-time administration [e.g., without the CD40 antigen-binding molecule and/or the CD40 inhibitor]).

[01276] In some embodiments, when the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered prior to, simultaneously with, and/or after the immunogen (e.g., an

immunogenic delivery vehicle), the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, eleven times, twelve times, thirteen times, fourteen times, fifteen times, sixteen times, seventeen times, eighteen times, nineteen times, or twenty times or more, prior to, simultaneously with, and/or after the administration of the immunogen (e.g., an immunogenic delivery vehicle). In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered seven days prior to the administration of the immunogen (e.g., an immunogenic delivery vehicle). In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered three days prior to the administration of the immunogen (e.g., an immunogenic delivery vehicle). In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered the same day as the administration of the immunogen (e.g., an immunogenic delivery vehicle). In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered one day after the administration of the immunogen (e.g., an immunogenic delivery vehicle). In some embodiments, when an immunogen is administered in accordance with a repeat dosing regimen, a CD40 antigen-binding molecule and/or a CD40 inhibitor may be administered any number of times prior to, simultaneously with, and/or after a first and/or second administration of the immunogen, and/or any number of subsequent administrations of the immunogen thereafter. Without wishing to be bound by theory, when a CD40 inhibitor is administered to inhibit an immune response to an immunogen in a subject in need thereof, e.g., an anti-drug antibody response to an immunogenic protein, the CD40 inhibitor may be co-administered (e.g., administered prior to, simultaneously with, and/or after the immunogen) to prevent the response of the immune system of the subject on each dose of the immunogen. As an example, an immunogen comprising a bacterial IgG cleaving enzyme IdeS/imlifidase may be administered to a subject for overcoming AAV pre-existing immunity; however, IdeS itself is immunogenic and can only be administered once. Co-administration of a CD40 inhibitor described herein with IdeS/imlifidase can prevent the de novo response to IdeS protein.

[01277] According to certain embodiments of the present disclosure, a CD40 antigen-binding molecule and/or a CD40 inhibitor may be administered to a subject separately from an immunogen (e.g., an immunogenic delivery vehicle) described herein.

[01278] In some embodiments, when a CD40 antigen-binding molecule and/or a CD40 inhibitor and an immunogen (e.g., an immunogenic delivery vehicle) are administered separately, the CD40 antigen-binding molecule and/or the CD40 inhibitor may be administered simultaneously with the administration of the immunogen. In some embodiments, the CD40 antigen-binding

molecule and/or the CD40 inhibitor is administered one or more times during the administration of the immunogen. In some embodiments, the immunogen is administered one or more times during the administration of the CD40 antigen-binding molecule and/or the CD40 inhibitor.

[01279] In some embodiments, a CD40 antigen-binding molecule and/or a CD40 inhibitor and an immunogen (e.g., an immunogenic delivery vehicle) may be administered separately over a defined time course. In certain embodiments, multiple doses of a CD40 antigen-binding molecule and/or a CD40 inhibitor and/or an immunogen (e.g., an immunogenic delivery vehicle) described herein may be administered to a subject over a defined time course. The methods according to such aspects of the disclosure may comprise sequentially administering to a subject multiple doses of a CD40 antigen-binding molecule and/or a CD40 inhibitor and/or immunogen of the disclosure. In some embodiments, when the CD40 antigen-binding molecule and/or the CD40 inhibitor and immunogen are administered sequentially, the CD40 antigen-binding molecule and/or the CD40 inhibitor can be administered before and/or in between each of the administrations of the immunogen(s). As used herein, "sequentially administering" means that each dose of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogenic delivery vehicle, is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks, months, or years). In some embodiments, the methods of the disclosure comprise sequentially administering to the subject a single initial dose of the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen, followed by one or more secondary doses of the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen (e.g., an immunogenic delivery vehicle), and optionally followed by one or more tertiary doses of the CD40 antigen-binding molecule and/or the CD40 inhibitor and/or the immunogen.

[01280] The terms "initial dose," "secondary dose(s)," and "tertiary dose(s)" refer to the temporal sequence of administration of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle). Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "loading dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. In some embodiments, the initial, secondary, and tertiary doses may all contain the same amount of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen but may differ from one another in terms of frequency of administration. In some embodiments, the amount of the CD40 antigen-binding molecule, CD40 inhibitor, and/or the immunogen contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down

as appropriate) during the course of treatment. In certain embodiments, one or more (e.g., 1, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses"). In some embodiments, the initial dose and the one or more secondary doses each contain the same amount of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen. In other embodiments, the initial dose comprises a first amount of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle) and the one or more secondary doses each comprise a second amount of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen. For example, the first amount of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle) can be 1.5x, 2x, 2.5x, 3x, 3.5x, 4x, 5x or more than the second amount of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen.

[01281] In some embodiments, each secondary and/or tertiary dose is administered 1 to 14 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of the CD40 antigen-binding molecule, the CD40 inhibitor, and/or the immunogen (e.g., an immunogenic delivery vehicle) that is administered to a subject prior to the administration of the very next dose in the sequence with no intervening doses.

[01282] The methods of the disclosure may comprise administering to a subject any number of secondary and/or tertiary doses of a CD40 antigen-binding molecule, a CD40 inhibitor, and/or an immunogen (e.g., an immunogenic delivery vehicle). For example, in certain embodiments, only a single secondary dose is administered to the subject. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the subject. Likewise, in certain embodiments, only a single tertiary dose is administered to the subject. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the subject.

[01283] In some embodiments involving multiple secondary doses, each secondary dose is administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the subject 1, 2, 3, or 4 weeks after the immediately preceding dose. Similarly, in some embodiments involving multiple tertiary doses, each tertiary dose is administered at the same frequency as the other tertiary doses. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a subject can vary

over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual subject following clinical examination.

[01284] In some embodiments, an amount of a plasma cell depleting agent, e.g., an antigen-binding molecule that binds to B cell maturation antigen (BCMA) and CD3 (e.g., an anti-BCMAxCD3 bispecific antibody), a B cell depleting agent (e.g., anti-CD19 and anti-CD20 antibodies, or a CD20xCD3 antigen-binding molecule (e.g., REGN1979)) (i.e., in combination with a plasma cell depleting agent), an immunoglobulin depleting agent such as a neonatal Fc receptor (FcRn) blocker (e.g., efgartigimod alfa) (i.e., in combination with a plasma cell depleting agent), or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), or pharmaceutical composition thereof, which is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) according to the methods disclosed herein is a therapeutically effective amount. In some embodiments, the plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody), the B cell depleting agent (e.g., anti-CD19/CD20 antibodies, or a CD20xCD3 antigen-binding molecule (e.g., REGN1979)) (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (e.g., efgartigimod alfa) (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), or pharmaceutical composition thereof, is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) as a weight-based dose. A "weight-based dose" (e.g., a dose in mg/kg) is a dose of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) that will change depending on the subject's weight.

[01285] Whenever administration of a plasma cell depleting agent, a B cell depleting agent, or an immunoglobulin depleting agent is discussed in this disclosure, it is in the context of being administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). Likewise, whenever administration of a B cell depleting agent or an immunoglobulin depleting agent is discussed in this disclosure, it is in the context of being administered in combination with a plasma cell depleting agent.

[01286] In other embodiments, the plasma cell depleting agent (e.g., an anti-BCMAxCD3

bispecific antibody), the B cell depleting agent (e.g., anti-CD19/CD20 antibodies, or a CD20xCD3 antigen-binding molecule (e.g., REGN1979)) (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (e.g., efgartigimod alfa) (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) as a fixed dose. A "fixed dose" (e.g., a dose in mg) means that one dose of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), is used for all subjects regardless of any specific subject-related factors, such as weight. In one particular embodiment, a fixed dose of a plasma cell depleting agent, a B cell depleting agent (i.e., in combination with a plasma cell depleting agent), an immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), is based on a predetermined weight or age.

[01287] Typically, a suitable dose of the plasma cell depleting agent, a B cell depleting agent (i.e., in combination with a plasma cell depleting agent), an immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can be in the range of about 0.001 to about 200.0 milligram per kilogram body weight of the recipient, generally in the range of about 1 to 50 mg per kilogram body weight. For example, the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) dose can be about 0.1 mg/kg, about 0.2 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 1.5 mg/kg, about 2 mg/kg, about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 25 mg/kg, about 30 mg/kg, about 40 mg/kg, or about 50 mg/kg per single dose. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[01288] In some embodiments, the plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody) is administered to a subject with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at a dose of about 25, about 20 to about 30, about 15 to about 35, about 10 to about 40, about 10 to about 25, about 15 to about 25, about 20 to about

25, about 25 to about 30, about 25 to about 35, or about 25 to about 40 mg/kg. In some embodiments, the plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody) is administered at a dose of about 20 to about 30 mg/kg. In some embodiments, the plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody) is administered at a dose of about 25 mg/kg.

[01289] In some embodiments, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 20, about 15 to about 25, about 10 to about 30, about 5 to about 35, about 5 to about 20, about 10 to about 20, about 15 to about 20, about 20 to about 25, about 20 to about 30, or about 20 to about 35 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 10 to about 20 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 25 to about 24 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 20 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 10 mg/kg (i.e., in combination with a plasma cell depleting agent).

[01290] In various embodiments, such as when a dose of an immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered in combination with a plasma cell depleting agent, and optionally, an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), described herein, the first dose of the immunoglobulin depleting agent may be delayed as compared to the first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 5 to about 20 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 7 to about 15 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 9 to about 11 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 10 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 11 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is

delayed by about 12 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 13 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 14 days as compared to first dose of the plasma cell depleting agent.

[01291] In one specific embodiment, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 10 mg/kg weekly for about 4 weeks and the first dose of the immunoglobulin depleting agent is delayed by about 9 to about 11 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 9 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 10 days as compared to first dose of the plasma cell depleting agent. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 11 days as compared to first dose of the plasma cell depleting agent.

[01292] In various embodiments, such as when a dose of an immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered, e.g., in combination with a plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody), a B cell depleting agent (e.g., an anti-CD20xCD3 bispecific antibody), and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), described herein, the first dose of the immunoglobulin depleting agent may be delayed as compared to the first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. The first dose of the immunoglobulin depleting agent being delayed as compared to the first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen may minimize the impact of the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) on the antibody drug half-life due to the e.g., FcRn blockade and/or the development of cross-reactive anti-drug antibodies.

[01293] In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 5 to about 20 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 7 to about 15 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 9 to about 11 days as

compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 10 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 11 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 12 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 13 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 14 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen.

[01294] In one specific embodiment, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 10 mg/kg weekly for about 4 weeks and the first dose of the immunoglobulin depleting agent is delayed by about 9 to about 11 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 9 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 10 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 11 days as compared to first dose of the plasma cell depleting agent, the first dose of the B cell depleting agent, and/or the first dose of the immunogen.

[01295] In various embodiments, such as when a dose of an immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered, e.g., in combination with an anti-CD40 antibody, described herein, the first dose of the immunoglobulin depleting agent may be delayed as compared to the first dose of the anti-CD40 antibody. The first dose of the immunoglobulin depleting agent being delayed as compared to the first dose of the anti-CD40 antibody may minimize the impact of the immunoglobulin depleting agent (e.g., FcRn blocker,

such as efgartigimod alfa) on the antibody drug half-life due to the e.g., FcRn blockade and/or the development of cross-reactive anti-drug antibodies.

[01296] In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 5 to about 20 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 7 to about 15 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 9 to about 11 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 10 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 11 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 12 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 13 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 14 days as compared to first dose of the anti-CD40 antibody.

[01297] In one specific embodiment, the immunoglobulin depleting agent (e.g., FcRn blocker, such as efgartigimod alfa) is administered at a dose of about 10 mg/kg weekly for about 4 weeks and the first dose of the immunoglobulin depleting agent is delayed by about 9 to about 11 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 9 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 10 days as compared to first dose of the anti-CD40 antibody. In some embodiments, the first dose of the immunoglobulin depleting agent is delayed by about 11 days as compared to first dose of the anti-CD40 antibody.

[01298] In some embodiments, the B cell depleting agent (e.g., anti-CD19 antibody or anti-CD20 antibody) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at a dose of about 20, about 15 to about 25, about 10 to about 30, about 5 to about 35, about 5 to about 20, about 10 to about 20, about 15 to about 20, about 20 to about 25, about 20 to about 30, or about 20 to about 35 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD19 antibody or anti-CD20 antibody) is administered at a dose of about 10 to about 20 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting

agent (e.g., anti-CD19 antibody or anti-CD20 antibody) is administered at a dose of about 25 to about 24 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD19 antibody or anti-CD20 antibody) is administered at a dose of about 20 mg/kg (i.e., in combination with a plasma cell depleting agent).

[01299] In some embodiments, the B cell depleting agent (e.g., anti-CD20xCD3 bispecific antibody) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at a dose of about 0.4 to about 0.6, 0.3 to about 0.7, 0.2, to about 0.8, 0.1 to about 1, 0.1 to about 0.9, 0.1 to about 0.5, 0.2 to about 0.5, 0.3 to about 0.5, 0.4 to about 0.5, 0.5 to about 0.6, 0.5 to about 0.7, 0.5 to about 0.8, 0.5 to about 0.9, or 0.5 to about 1 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD20xCD3 bispecific antibody) is administered at a dose of about 0.4 to about 0.6 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD20xCD3 bispecific antibody) is administered at a dose of about 0.3 to about 0.7 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD20xCD3 bispecific antibody) is administered at a dose of about 0.5 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD20xCD3 bispecific antibody) is administered at a dose of about 0.1 mg/kg (i.e., in combination with a plasma cell depleting agent). In some embodiments, the B cell depleting agent (e.g., anti-CD20xCD3 bispecific antibody) is administered at a dose of about 1 mg/kg (i.e., in combination with a plasma cell depleting agent).

[01300] In some embodiments, the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or optionally the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) as a fixed dose of between about 5 mg to about 2500 mg. In some embodiments, the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent) is administered as a fixed dose of about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg,

about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1500 mg, about 2000 mg, or about 2500 mg. Values and ranges intermediate to the recited values are also intended to be part of this disclosure.

[01301] In one embodiment, for a plasma cell depleting agent (e.g., an anti-BCMA/anti-CD3 bispecific antibody), a therapeutically effective amount can be from about 0.05 mg to about 500 mg, from about 1 mg to about 500 mg, from about 10 mg to about 450 mg, from about 50 mg to about 400 mg, from about 75 mg to about 350 mg, or from about 100 mg to about 300 mg of the antibody. For example, in various embodiments, the amount of the plasma cell depleting agent is about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg, of the plasma cell depleting agent.

[01302] In some embodiments, the plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody), the B cell depleting agent (e.g., anti-CD19/CD20 antibodies, or a CD20xCD3 antigen-binding molecule (e.g., REGN1979)) (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (e.g., efgartigimod alfa) (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can be administered at a dosing frequency of about four times a week, twice a week, once a week,

once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can be administered at a dosing frequency of about four times a year, twice a year, once a week, once every two years, once every three years, once every four years, once every five years, once every six years, once every eight years, once every twelve years, or less frequently so long as a therapeutic response is achieved.

[01303] Dose ranges and frequency of administration of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) described herein can vary depending on the nature of, and/or the medical condition, as well as parameters of a specific subject and the route of administration used. As a non-limiting example, immunogenic delivery vehicle (e.g., AAV vector) compositions can be administered to a subject at a dose ranging from about 1×10^5 plaque forming units (pfu) to about 1×10^{15} pfu, depending on mode of administration, the route of administration, the nature of the disease and condition of the subject. In some cases, the immunogenic delivery vehicle (e.g., AAV vector) compositions can be administered at a dose ranging from about 1×10^8 pfu to about 1×10^{15} pfu, or from about 1×10^{10} pfu to about 1×10^{15} pfu, or from about 1×10^8 pfu to about 1×10^{12} pfu. A more accurate dose can also depend on the subject in which it is being administered. For example, a lower dose may be required if the subject is juvenile, and a higher dose may be required if the subject is an adult human subject. In certain embodiments, a more accurate dose can depend on the weight of the subject. In certain embodiments, for example, a juvenile human subject can receive from about 1×10^8 pfu to about 1×10^{10} pfu, while an adult human subject can receive a dose from about 1×10^{10} pfu to about 1×10^{12} pfu.

[01304] In some embodiments, multiple doses of a plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody), a B cell depleting agent (e.g., anti-CD19/CD20 antibodies, or a CD20xCD3 antigen-binding molecule (e.g., REGN1979)) (i.e., in combination with a plasma cell depleting agent), an immunoglobulin depleting agent (e.g., efgartigimod alfa) (i.e., in combination with a plasma cell depleting agent), or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) are administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) over a defined time course. In some embodiments, the methods of the present disclosure comprise sequentially administering to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be

administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) multiple doses of the plasma cell depleting agent (e.g., an anti-BCMAxCD3 bispecific antibody), the B cell depleting agent (e.g., anti-CD19/CD20 antibodies, or a CD20xCD3 antigen-binding molecule (e.g., REGN1979)) (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (e.g., efgartigimod alfa) (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01305] In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be administered in accordance with a repeat dosing regimen wherein the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be administered a first time (e.g., in an initial dose) and then re-administered any number of subsequent times thereafter at any amount over the time course of treatment of a subject. For example, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be re-administered once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more, over the time course of the treatment of a subject which can occur over any number of days, weeks, or years. In some embodiments, when the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprises a vector, e.g., a viral vector such as an AAV vector, the vector which is administered first in a repeat dosing regimen may comprise the same vector which is re-administered second in the repeat dosing regimen, or any number of subsequent times thereafter. In some embodiments, when the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprises a vector, e.g., a viral vector such as an AAV vector, the vector which is administered first in a repeat dosing regimen may comprise a different vector than is re-administered second in the repeat dosing regimen, or any number of subsequent times thereafter.

[01306] In some embodiments, an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), e.g., a viral vector such as an AAV vector, may be administered in accordance with a stepwise dosing regimen. Stepwise dosing of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can refer to breaking up (i.e., dividing) dosing of the same immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) over multiple administrations. In some embodiments, the dosing of the same immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is broken up once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more, over the time course of the treatment of a subject which can occur over any number of days, weeks, or years. In some embodiments, when a stepwise dose regimen is used in the administration of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), the stepwise dosing

regimen may result in a gradual increase in therapeutic transgene levels with each administration of the immunogen (e.g., in an immunogenic delivery vehicle such as, e.g., AAV). Without wishing to be bound by theory, a stepwise dosing regimen used in the administration of an immunogen (e.g., in an immunogenic delivery vehicle such as, e.g., AAV) comprising an immunogen (e.g., in an immunogenic delivery vehicle such as, e.g., AAV), e.g., a viral vector such as an AAV vector, can result in enhanced control over transgene expression in a cell and/or subject, since for some transgenes too much expression can result in its own pathology.

[01307] In some embodiments, an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is administered to a subject with preexisting immunity against an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) in combination with a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent). The plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) can be administered prior to, simultaneously with, or after the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In one example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered prior to the immunogen (e.g., an immunogenic delivery vehicles such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered prior to and after the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered simultaneously with the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the plasma cell depleting agent is administered before the administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, such as when the immunogen is administered two or more times, the plasma cell depleting agent is administered before and/or between each of the administrations of the immunogen. In some embodiments, the plasma cell depleting agent is administered again within a short period of the first administration. In some embodiments, the plasma cell depleting agent is continuously administered throughout the pre-dose and re-dose periods (e.g., to clear plasma cells and keep plasma cell levels low).

[01308] In some embodiments, when the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered prior to, simultaneously with, and/or after the immunogen (e.g., an immunogenic delivery vehicle

such as, e.g., AAV), the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, eleven times, twelve times, thirteen times, fourteen times, fifteen times, sixteen times, seventeen times, eighteen times, nineteen times, or twenty times or more, prior to, simultaneously with, and/or after the administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, when an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is administered in accordance with a repeat dosing regimen, a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) may be administered any number of times prior to, simultaneously with, and/or after a first and/or second administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), and/or any number of subsequent administrations of the immunogen thereafter. Without wishing to be bound by theory, when a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) is administered to inhibit an immune response to an immunogen (i.e., an immunogen to be administered to a subject, e.g., an immunogenic delivery vehicle) in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV), e.g., an anti-drug antibody response to an immunogenic protein, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) may be co-administered (e.g., administered prior to, simultaneously with, and/or after the immunogen) to prevent the response of the immune system of the subject on each dose of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). As an example, an immunogen comprising a bacterial IgG cleaving enzyme IdeS/imlifidase may be administered to a subject for overcoming AAV pre-existing immunity; however, IdeS itself is immunogenic and can only be administered once. Co-administration of a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) described herein with IdeS/imlifidase can prevent the de novo response to IdeS protein.

[01309] According to certain embodiments of the present disclosure, a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) may be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic

delivery vehicle such as, e.g., AAV) separately from an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) described herein.

[01310] In some embodiments, when a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) and an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) are administered separately, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) may be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with the administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) one or more times during the administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is administered one or more times during the administration of the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) (i.e., the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before the administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, such as when the immunogen is administered two or more times, the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before and/or between each of the administrations of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) again within a short period of the first administration. In some embodiments, the plasma cell depleting agent is continuously administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen

to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) throughout the pre-dose and re-dose periods (e.g., to clear plasma cells and keep plasma cell levels low).

[01311] In some embodiments, a B cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to a plasma cell depleting agent. In some embodiments, a B cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with a plasma cell depleting agent. In some embodiments, a B cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) subsequent to a plasma cell depleting agent. In some embodiments, a B cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to and subsequent to a plasma cell depleting agent. In some embodiments, a B cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to and simultaneously with a plasma cell depleting agent. In some embodiments, a B cell depleting agent is administered to a subject with preexisting immunity against an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with and subsequent to a plasma cell depleting agent. In theory, B cell depletion in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) could be conducted before or after plasma cell depletion with the same effect, provided that B cells remain depleted up until the time of dosing with the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01312] In some embodiments, an immunoglobulin depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) subsequent to a plasma cell depleting agent. In some embodiments, an immunoglobulin depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) subsequent to a B cell depleting agent. In some embodiments, an immunoglobulin depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an

immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) subsequent to a plasma cell depleting agent and a B cell depleting agent. For example, if the plasma cell depleting agent is an anti-BCMAxCD3 bispecific antibody, administering the immunoglobulin depleting agent after the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) will prevent more rapid clearance of the plasma cell depleting agent. For example, if the B cell depleting agent is an anti-CD20xCD3 bispecific antibody, administering the immunoglobulin depleting agent after the B cell depleting agent to a subject with preexisting immunity against an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) will prevent more rapid clearance of the B cell depleting agent. The timing can be affected by what immunoglobulin depleting agent is used. For example, different treatment regimens would be expected for FcRn blockers vs. IgG degrading enzymes (e.g., IdeS). IdeS is an enzyme and therefore acts much more rapidly than FcRn blockade, clearing IgGs within hours to days. For FcRn blockade, several weeks of treatment may be required to fully clear anti-AAV IgGs from circulation.

[01313] In some embodiments, a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) and an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) separately over a defined time course. In certain embodiments, multiple doses of a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) described herein may be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) over a defined time course. The methods according to such aspects of the disclosure may comprise sequentially administering to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject e.g., an immunogenic delivery vehicle such as, e.g., AAV) multiple doses of a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an immunoglobulin depleting agent) and/or immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) of the disclosure. In some embodiments, when the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) are administered sequentially, the plasma cell

depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before and/or in between each of the administrations of the immunogen(s) (e.g., an immunogenic delivery vehicle(s) such as, e.g., AAV).

[01314] As used herein, "sequentially administering" means that each dose of the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks, months, or years). In some embodiments, the methods of the disclosure comprise sequentially administering to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) a single initial dose of the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), followed by one or more secondary doses of the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), and optionally followed by one or more tertiary doses of the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01315] The terms "initial dose," "secondary dose(s)," and "tertiary dose(s)" refer to the temporal sequence of administration of the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "loading dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. In some embodiments, the initial, secondary, and tertiary doses may all contain the same amount of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination

with the plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with the plasma cell depleting agent), and/or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) but may differ from one another in terms of frequency of administration. In some embodiments, the amount of the plasma cell depleting agent, B cell depleting agent (i.e., in combination with a plasma cell depleting agent), immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) contained in the initial, secondary and/or tertiary doses varies from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, one or more (e.g., 1, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses"). In some embodiments, the initial dose and the one or more secondary doses each contain the same amount of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In other embodiments, the initial dose comprises a first amount of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) and the one or more secondary doses each comprise a second amount of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). For example, the first amount of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can be 1.5x, 2x, 2.5x, 3x, 3.5x, 4x, 5x or more than the second amount of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01316] In some embodiments, each secondary and/or tertiary dose is administered 1 to 14 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the

immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of the plasma cell depleting agent, the B cell depleting agent (i.e., in combination with a plasma cell depleting agent), the immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) that is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to the administration of the very next dose in the sequence with no intervening doses.

[01317] The methods of the disclosure may comprise administering to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) any number of secondary and/or tertiary doses of a plasma cell depleting agent, a B cell depleting agent (i.e., in combination with a plasma cell depleting agent), an immunoglobulin depleting agent (i.e., in combination with a plasma cell depleting agent), or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). For example, in certain embodiments, only a single secondary dose is administered to the subject. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the subject. Likewise, in certain embodiments, only a single tertiary dose is administered to the subject. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the subject.

[01318] In some embodiments involving multiple secondary doses, each secondary dose is administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the subject 1, 2, 3, or 4 weeks after the immediately preceding dose. Similarly, in some embodiments involving multiple tertiary doses, each tertiary dose is administered at the same frequency as the other tertiary doses. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a subject can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual subject following clinical examination.

[01319] In some embodiments, the secondary and/or tertiary doses of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprising a viral particle or vector (e.g., a viral vector such as an AAV vector) administered to the subject is of the same or similar viral origin as the initial dose. In some embodiments, the secondary and/or tertiary doses of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprising a viral particle or vector (e.g., a viral vector such as an AAV vector) administered to the subject is of a

different viral origin then the initial dose.

[01320] In some embodiments, the subsequently administered immunogenic delivery vehicle (e.g., a viral vector such as an AAV vector) is administered via the same administration route as the originally administered immunogenic delivery vehicle (e.g., a viral vector such as an AAV vector) .

[01321] In some embodiments, when a plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) herein are sequentially administered, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be administered as a first component of the dosing regimen and the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) may be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) as a second component of the dosing regimen (i.e., the immunogen (e.g., an immunogenic delivery vehicle) may be administered before the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent)). In some embodiments, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be administered as a second component of the dosing regimen and the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) may be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) as a first component of a dosing regimen (i.e., an immunogenic delivery vehicle such as, e.g., AAV) may be administered after the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent). In some embodiments, an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) and a plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) may be sequentially administered, in either of the above-described orders, with variable time intervals between administration. For example, the time interval between administration of the immunogen (e.g., an immunogenic delivery vehicle) (e.g., an immunogenic delivery vehicle such as, e.g., AAV) and the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) may be at least about 30 seconds, at least about 35 seconds, at least about 40 seconds, at least about 45 seconds, at least about 50 seconds, at least about 55 seconds, at least about 1 minute, at least about 2 minutes, at least about 5

minutes, at least about 10 minutes, at least about 20 minutes, at least about 30 minutes, at least about 40 minutes, at least about 50 minutes, at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 10 to 12 hours, at least about 12 to 14 hours, at least about 14 to 16 hours, at least about 16 to 18 hours, at least about 18 to 20 hours, at least about 20 to 22 hours, at least about 22 to 24 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 7 days, at least about 8 days, at least about 9 days, at least about 10 days, at least about 10 to 12 days, at least about 12 to 14 days, at least about 14 to 16 days, at least about 16 to 18 days, at least about 18 to 20 days, at least about 20 to 22 days, at least about 22 to 24 days, at least about 24 to 26 days, at least about 28 days, at least about 29 days, at least about 30 days, at least about 31 days, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more.

[01322] Any of the above methods can further comprise any of various subsequent administration steps described herein. The subsequent administration step can comprise, for example, administering the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) and an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) to the subject one or more subsequent times until a desired level of expression and/or activity of the polypeptide of interest is achieved in the subject.

[01323] The subsequent administration step can be, for example, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 9 weeks, at least about 10 weeks, at least about 11 weeks, or at least about 12 weeks after the initial dosing (e.g., at least about 4 weeks after the initial dosing) or about 4 weeks to about 12 weeks, about 4 weeks to about 13 weeks, about 4 weeks to about 14 weeks, about 4 weeks to about 15 weeks, about 4 weeks to about 16 weeks, about 1 week to about 12 weeks, about 2 weeks to about 12 weeks, about 3 weeks to about 12 weeks, about 1 week to about 15 weeks, about 2

week to about 14 weeks, or about 3 weeks to about 13 weeks after the initial dosing (e.g., about 4 weeks to about 12 weeks after the initial dosing).

[01324] The subsequent administration step can be, for example, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 9 weeks, at least about 10 weeks, at least about 11 weeks, or at least about 12 weeks after the initial dosing (e.g., at least about 4 weeks after the initial dosing) or about 4 weeks to about 12 weeks, about 4 weeks to about 13 weeks, about 4 weeks to about 14 weeks, about 4 weeks to about 15 weeks, about 4 weeks to about 16 weeks, about 1 week to about 12 weeks, about 2 weeks to about 12 weeks, about 3 weeks to about 12 weeks, about 1 week to about 15 weeks, about 2 week to about 14 weeks, or about 3 weeks to about 13 weeks after the initial dosing (e.g., about 4 weeks to about 12 weeks after the initial dosing).

[01325] The subsequent administration step can comprise, for example, administering a second immunogen, e.g., an immunogenic delivery vehicle such as a vector, e.g., a viral vector such as, e.g., an AAV vector, comprising a coding sequence for a second polypeptide of interest (e.g., that is different from a first polypeptide of interest encoded by a first immunogenic delivery vehicle such as a vector, e.g., a viral vector such as, e.g., an AAV vector administered in an initial administration step) to the subject one or more subsequent times until a desired level of expression and/or activity of the polypeptide of interest is achieved in the subject.

[01326] The subsequent administration step can be, for example, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 9 weeks, at least about 10 weeks, at least about 11 weeks, or at least about 12 weeks after the initial dosing (e.g., at least about 4 weeks after the initial dosing) or about 4 weeks to about 12 weeks, about 4 weeks to about 13 weeks, about 4 weeks to about 14 weeks, about 4 weeks to about 15 weeks, about 4 weeks to about 16 weeks, about 1 week to about 12 weeks, about 2 weeks to about 12 weeks, about 3 weeks to about 12 weeks, about 1 week to about 15 weeks, about 2 week to about 14 weeks, or about 3 weeks to about 13 weeks after the initial dosing (e.g., about 4 weeks to about 12 weeks after the initial dosing).

[01327] In some embodiments, the present disclosure provides a method for increasing effectiveness of administration of a subsequently administered immunogen, e.g., an immunogenic delivery vehicle such as a vector, e.g., a viral vector such as, e.g., an AAV vector, in a subject in need thereof, comprising administering to the subject an effective amount of a plasma cell depleting agent (optionally in combination with a B cell depleting agent and/or an

immunoglobulin depleting agent) to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV), and the subsequently administered immunogen, e.g., an immunogenic delivery vehicle such as a vector, e.g., a viral vector such as, e.g., an AAV vector, is of the same or similar viral origin as the originally administered immunogenic delivery vehicle such as a vector, e.g., a viral vector such as, e.g., an AAV vector.

[01328] In some embodiments, the subsequently administered immunogenic delivery vehicle (e.g., a viral vector such as an AAV vector) is administered via the same administration route as the originally administered immunogenic delivery vehicle (e.g., a viral vector such as an AAV vector).

[01329] In some embodiments, the subsequently administered immunogenic delivery vehicle (e.g., a viral vector such as an AAV vector) is administered via a different administration route from the originally administered immunogenic delivery vehicle (e.g., a viral vector such as an AAV vector).

[01330] In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before the administration of the viral vector(s).

[01331] In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with the administration of the viral vector(s).

[01332] In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) after the administration of the viral vector(s).

[01333] In some embodiments, the viral vectors are administered two or more times and the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before and/or between each of the administrations of the

viral vectors.

[01334] In some embodiments, the immunogen re-administration occurs via the same administration route as its prior administration. In some embodiments, the immunogen re-administration occurs via a different administration route than its prior administration. In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject. In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject. In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before the administration of the immunogen. In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with the administration of the immunogen. In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) after the administration of the immunogen. In some embodiments, the immunogen is administered two or more times and the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before and/or between each of the administrations of the immunogen. In some embodiments, the plasma cell depleting agent is administered before the administration of the immunogen. In some embodiments, the plasma cell depleting agent is administered again within a short period of the first administration. In some embodiments, the plasma cell depleting agent is continuously administered throughout the pre-dose and re-dose periods (e.g., to clear plasma cells and keep plasma cell levels low).

[01335] In any of the above methods, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with the immunogen (e.g., in an immunogenic delivery vehicle) (e.g., an

immunogenic delivery vehicle such as, e.g., AAV) or not simultaneously (e.g., sequentially in any combination). For example, in a method comprising administering a composition comprising a plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) and an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), they can be administered separately (e.g., the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) separately from the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). For example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), subsequent to the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), prior to and subsequent to the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), or at the same time as immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) before the administration of the immunogen. In some embodiments, the plasma cell depleting agent is administered again to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within a short period of the first administration. In some embodiments, the plasma cell depleting agent is continuously administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) throughout the pre-dose and re-dose periods (e.g., to clear plasma cells and keep plasma cell levels low).

[01336] In some embodiments, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 hour to about 48 hours, about 1 hour to about 24 hours, about 1 hour to about 12 hours, about 1 hour to about 6 hours, about 1 hour to about 2 hours, about 2 hours to about 48 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 2 hours to about 6 hours, about 3 hours to about 48 hours, about 6 hours to about 48 hours, about 12 hours to about 48 hours,

or about 24 hours to about 48 hours prior to and/or subsequent to administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01337] In one example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and/or subsequent to administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01338] In one example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to and subsequent to administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the

plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to and subsequent to administering immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and subsequent to administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01339] In one example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week after administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week after administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In another example, the plasma cell depleting agent (optionally in combination with the B cell depleting agent and/or the immunoglobulin depleting agent) is administered to a subject

with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days after administering the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01340] In some embodiments, the secondary and/or tertiary doses of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprising a viral particle or vector (e.g., a viral vector such as an AAV vector) administered to the subject is of the same or similar viral origin as the initial dose. In some embodiments, the secondary and/or tertiary doses of an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprising a viral particle or vector administered to the subject is of a different viral origin then the initial dose.

[01341] In some embodiments, the subsequently administered viral vector is administered via the same administration route as the originally administered viral vector. In some embodiments, the subsequently administered viral vector is administered via a different administration route from the originally administered viral vector.

[01342] In some embodiments, when a CD40 antigen-binding molecule, and/or a CD40 inhibitor and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) herein are sequentially administered, the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) may be administered as a first component of the dosing regimen and the CD40 antigen-binding molecule and/or CD40 inhibitor may be administered as a second component of the dosing regimen (i.e., the immunogen may be administered before the CD40 antigen-binding molecule and/or the CD40 inhibitor). In some embodiments, the immunogen may be administered as a second component of the dosing regimen and the CD40 antigen-binding molecule and/or the CD40 inhibitor may be administered as a first component of a dosing regimen (i.e., the immunogen may be administered after the CD40 antigen-binding molecule and/or the CD40 inhibitor). In some embodiments, an immunogen and a CD40 antigen-binding molecule and/or a CD40 inhibitor may be sequentially administered, in either of the above-described orders, with variable time intervals between administration. For example, the time interval between administration of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) and the CD40 antigen-binding molecule and/or CD40 inhibitor may

be at least about 30 seconds, at least about 35 seconds, at least about 40 seconds, at least about 45 seconds, at least about 50 seconds, at least about 55 seconds, at least about 1 minute, at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, at least about 30 minutes, at least about 40 minutes, at least about 50 minutes, at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 10 to 12 hours, at least about 12 to 14 hours, at least about 14 to 16 hours, at least about 16 to 18 hours, at least about 18 to 20 hours, at least about 20 to 22 hours, at least about 22 to 24 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, at least about 7 days, at least about 8 days, at least about 9 days, at least about 10 days, at least about 10 to 12 days, at least about 12 to 14 days, at least about 14 to 16 days, at least about 16 to 18 days, at least about 18 to 20 days, at least about 20 to 22 days, at least about 22 to 24 days, at least about 24 to 26 days, at least about 28 days, at least about 29 days, at least about 30 days, at least about 31 days, at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, at least about 5 years, at least about 6 years, at least about 7 years, at least about 8 years, at least about 9 years, at least about 10 years, or more.

[01343] Any of the above methods can further comprise any of various subsequent administration steps described herein. The subsequent administration step can comprise, for example, administering the CD40 antigen binding molecule and/or the CD40 inhibitor and an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) to the subject one or more subsequent times until a desired level of expression and/or activity of the polypeptide of interest is achieved in the subject.

[01344] The subsequent administration step can be, for example, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 9 weeks, at least about 10 weeks, at least about 11 weeks, or at least about 12 weeks after the initial dosing (e.g., at least about 4 weeks after the initial dosing) or about 4 weeks to about 12 weeks, about 4 weeks to about 13 weeks, about 4 weeks to about 14 weeks, about 4 weeks to about 15 weeks, about 4 weeks to about 16 weeks, about 1 week to about 12 weeks, about 2 weeks to

about 12 weeks, about 3 weeks to about 12 weeks, about 1 week to about 15 weeks, about 2 week to about 14 weeks, or about 3 weeks to about 13 weeks after the initial dosing (e.g., about 4 weeks to about 12 weeks after the initial dosing).

[01345] The subsequent administration step can be, for example, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 9 weeks, at least about 10 weeks, at least about 11 weeks, or at least about 12 weeks after the initial dosing (e.g., at least about 4 weeks after the initial dosing) or about 4 weeks to about 12 weeks, about 4 weeks to about 13 weeks, about 4 weeks to about 14 weeks, about 4 weeks to about 15 weeks, about 4 weeks to about 16 weeks, about 1 week to about 12 weeks, about 2 weeks to about 12 weeks, about 3 weeks to about 12 weeks, about 1 week to about 15 weeks, about 2 week to about 14 weeks, or about 3 weeks to about 13 weeks after the initial dosing (e.g., about 4 weeks to about 12 weeks after the initial dosing).

[01346] The subsequent administration step can comprise, for example, administering a second immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), e.g. an immune delivery vehicle comprising, e.g., a vector comprising a coding sequence for a second polypeptide of interest (e.g., that is different from a first polypeptide of interest encoded by a first vector administered in an initial administration step) to the subject one or more subsequent times until a desired level of expression and/or activity of the polypeptide of interest is achieved in the subject.

[01347] The subsequent administration step can be, for example, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 5 weeks, at least about 6 weeks, at least about 7 weeks, at least about 8 weeks, at least about 9 weeks, at least about 10 weeks, at least about 11 weeks, or at least about 12 weeks after the initial dosing (e.g., at least about 4 weeks after the initial dosing) or about 4 weeks to about 12 weeks, about 4 weeks to about 13 weeks, about 4 weeks to about 14 weeks, about 4 weeks to about 15 weeks, about 4 weeks to about 16 weeks, about 1 week to about 12 weeks, about 2 weeks to about 12 weeks, about 3 weeks to about 12 weeks, about 1 week to about 15 weeks, about 2 week to about 14 weeks, or about 3 weeks to about 13 weeks after the initial dosing (e.g., about 4 weeks to about 12 weeks after the initial dosing).

[01348] In some embodiments, the present disclosure provides a method for increasing effectiveness of a subsequently administered viral vector following an originally administered viral vector in a subject in need thereof, comprising administering to the subject an effective

amount of a CD40 inhibitor, and the subsequently administered viral vector is of the same or similar viral origin as the originally administered viral vector.

[01349] In some embodiments, the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject. In some embodiments, the method comprises determining the level of non-neutralizing antibodies in the subject.

[01350] In some embodiments, the subsequently administered viral vector is administered via the same administration route as the originally administered viral vector.

[01351] In some embodiments, the subsequently administered viral vector is administered via a different administration route from the originally administered viral vector.

[01352] In some embodiments, the plasma cell depleting agent is administered before the administration of the subsequently administered viral vector(s).

[01353] In some embodiments, the plasma cell depleting agent is administered simultaneously with the administration of the subsequently administered viral vector(s).

[01354] In some embodiments, the subsequently administered viral vectors are administered two or more times and the plasma cell depleting agent is administered before and/or between each of the administrations of the subsequently administered viral vectors.

[01355] In some embodiments, the CD40 inhibitor is administered before the administration of the viral vector(s). In some embodiments, the CD40 inhibitor is administered before the originally administered viral vector to the subject.

[01356] In some embodiments, the CD40 inhibitor is administered simultaneously with the administration of the viral vector(s). In some embodiments, the CD40 inhibitor is administered simultaneously with the administration of the originally administered viral vector and/or subsequently administered viral vector to the subject.

[01357] In some embodiments, the CD40 inhibitor is administered after the administration of the viral vector(s). In some embodiments, the CD40 inhibitor is administered after the administration of the originally administered viral vector but before administering the subsequently administered viral vector to the subject. In some embodiments, the CD40 inhibitor is administered after the administration of the subsequently administered viral vector to the subject.

[01358] In some embodiments, the viral vectors are administered two or more times and the CD40 inhibitor is administered before and/or between each of the administrations of the viral vectors.

[01359] In any of the above methods, the CD40 antigen-binding molecule and/or the CD40 inhibitor can be administered simultaneously with the immunogen (e.g., an immunogenic

delivery vehicle) or not simultaneously (e.g., sequentially in any combination). For example, in a method comprising administering a composition comprising a CD40 antigen-binding molecule and/or a CD40 inhibitor and an immunogen, they can be administered separately (e.g., the CD40 antigen-binding molecule and/or the CD40 inhibitor separately from the immunogen). For example, the CD40 antigen-binding molecule and/or CD40 inhibitor can be administered prior to the immunogen, subsequent to the immunogen, prior to and subsequent to the immunogen, or at the same time as immunogen. In some embodiments, such as when the immunogen is administered two or more times, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered before and/or between each of the administrations of the immunogen.

[01360] In some embodiments, the CD40 antigen-binding molecule and/or the CD40 inhibitor can be administered about 1 hour to about 48 hours, about 1 hour to about 24 hours, about 1 hour to about 12 hours, about 1 hour to about 6 hours, about 1 hour to about 2 hours, about 2 hours to about 48 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 2 hours to about 6 hours, about 3 hours to about 48 hours, about 6 hours to about 48 hours, about 12 hours to about 48 hours, or about 24 hours to about 48 hours prior to and/or subsequent to administration of the immunogen.

[01361] In one example, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or CD40 inhibitor is administered about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and/or subsequent to administering the immunogen (e.g., an immunogenic delivery vehicle).

[01362] In one example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is

administered about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to and subsequent to administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to and subsequent to administering immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and subsequent to administering the immunogen (e.g., an immunogenic delivery vehicle).

[01363] In one example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days after administering the immunogen (e.g., an immunogenic delivery vehicle).

[01364] In one example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered within about 1 month, within about 2 months, within about 3 months, within about 4

months, within about 5 months, within about 6 months, or within about 12 months after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered within about 6 months after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered about 1 to about 6 months, about 2 to about 6 months, about 3 to about 6 months, about 4 to about 6 months, about 5 to about 6 months, about 1 to about 5 months, about 1 to about 4 months, about 1 to about 3 months, or about 1 to about 2 months after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered more than 6 months after administering the immunogen (e.g., an immunogenic delivery vehicle). In another example, the CD40 antigen-binding molecule and/or the CD40 inhibitor is administered about 1 to about 12 months or about 6 months to about 12 months after administering the immunogen (e.g., an immunogenic delivery vehicle). In some methods, the method can comprise determining whether the immunogen (e.g., an immunogenic delivery vehicle) are present in the subject (e.g., from a previous administration).

[01365] In any of the above methods, a plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with the immunogen or not simultaneously (e.g., sequentially in any combination). For example, in a method comprising administering a composition or combination comprising a plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) and further comprising administering an immunogen , they can be administered separately (e.g., the plasma cell depleting agent or combination comprising the plasma cell depleting agent separately from the an immunogen). For example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to the immunogen, subsequent to the immunogen, prior to and subsequent to the immunogen, or at the same time as the immunogen. Any suitable

methods of administering plasma cell depleting agents or combinations comprising a plasma cell depleting agent and immunogen(s) to cells can be used, and examples of such methods are described in more detail elsewhere herein.

[01366] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 hour to about 48 hours, about 1 hour to about 24 hours, about 1 hour to about 12 hours, about 1 hour to about 6 hours, about 1 hour to about 2 hours, about 2 hours to about 48 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 2 hours to about 6 hours, about 3 hours to about 48 hours, about 6 hours to about 48 hours, about 12 hours to about 48 hours, or about 24 hours to about 48 hours prior to and/or subsequent to administration of the immunogen.

[01367] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to administering the immunogen.

[01368] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, or about 6 days to about 7 days prior to administering the immunogen.

[01369] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to and subsequent to administering immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at

least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to and subsequent to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and subsequent to administering the immunogen.

[01370] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week after administering immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days after administering the immunogen.

[01371] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 1 month, within about 2 months, within about 3 months, within about 4 months, within about 5 months, within about 6 months, or within about 12 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 6 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 6 months, about 2 to about 6 months, about 3 to about 6 months, about 4 to about 6 months, about 5 to about 6 months, about 1 to about 5 months, about 1 to about 4 months, about 1 to about 3 months, or about 1 to about 2 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) more than 6 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 12 months or about 6 months to about 12 months after administering the immunogen. In some methods, the method can comprise determining whether the immunogen is present in the subject (e.g., from a previous administration). The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the

immunogen is still present in the subject. For example, if the immunogen is a viral vector (or is delivered in a viral vector) (e.g., a recombinant AAV vector), the method can comprise determining whether the viral vector is present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the viral vector is still present (i.e., detectable) in the subject. For example, if the immunogen is a viral vector (or is delivered in a viral vector) (e.g., a recombinant AAV vector), the method can comprise determining whether viral capsid protein (e.g., AAV capsid protein) is present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the capsid protein is still present (i.e., detectable) in the subject. For example, if the immunogen is a lipid nanoparticle, the method can comprise determining whether the lipid nanoparticle components (e.g., PEG) are present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the lipid nanoparticle components are still present (i.e., detectable) in the subject. For example, if the immunogen is a lipid nanoparticle, the method can comprise determining whether certain lipid nanoparticle components are present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the components are still present (i.e., detectable) in the subject.

[01372] In methods in which a composition or combination comprising a plasma cell depleting agent or combination comprising the plasma cell depleting agent in combination with a CD40 inhibitor is administered, the plasma cell depleting agent or combination comprising the plasma cell depleting agent and the CD40 inhibitor can be administered simultaneously to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). Alternatively, the plasma cell depleting agent or combination comprising the plasma cell depleting agent and the CD40 inhibitor can be administered sequentially in any order. For example, the plasma cell depleting

agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to and/or after the CD40 inhibitor. In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to and after the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with and after the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with and before the CD40 inhibitor.

[01373] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 hour to about 48 hours, about 1 hour to about 24 hours, about 1 hour to about 12 hours, about 1 hour to about 6 hours, about 1 hour to about 2 hours, about 2 hours to about 48 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 2 hours to about 6 hours, about 3 hours to about 48 hours, about 6 hours to about 48 hours, about 12 hours to about 48 hours, or about 24 hours to about 48 hours prior to and/or subsequent to administration of the CD40 inhibitor.

[01374] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least

about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to administering the CD40 inhibitor.

[01375] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered within about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7

days, about 5 days to about 7 days, or about 6 days to about 7 days prior to administering the CD40 inhibitor.

[01376] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to and subsequent to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to and subsequent to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and subsequent to administering the CD40 inhibitor.

[01377] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at

least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days after administering the CD40 inhibitor.

[01378] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 1 month, within about 2 months, within about 3 months, within about 4 months, within about 5 months, within about 6 months, or within about 12 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 6 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 6 months, about 2 to about 6 months, about 3 to about 6 months, about 4 to about 6 months, about 5 to about 6 months, about 1 to about 5 months, about 1 to about 4 months, about 1 to about 3 months, or about 1 to about 2 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting

agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) more than 6 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 12 months or about 6 months to about 12 months after administering the CD40 inhibitor.

[01379] Administration *in vivo* can be by any suitable route including, for example, parenteral, intravenous, oral, subcutaneous, intra-arterial, intracranial, intrathecal, intratumoral, intraperitoneal, topical, intranasal, or intramuscular. Systemic modes of administration include, for example, oral and parenteral routes. Examples of parenteral routes include intravenous, intraarterial, intraosseous, intramuscular, intradermal, subcutaneous, intranasal, and intraperitoneal routes. A specific example is intravenous infusion. Nasal instillation and intravitreal injection are other specific examples. Local modes of administration include, for example, intrathecal, intracerebroventricular, intraparenchymal (e.g., localized intraparenchymal delivery to the striatum (e.g., into the caudate or into the putamen), cerebral cortex, precentral gyrus, hippocampus (e.g., into the dentate gyrus or CA3 region), temporal cortex, amygdala, frontal cortex, thalamus, cerebellum, medulla, hypothalamus, tectum, tegmentum, or substantia nigra), intraocular, intraorbital, subconjunctival, intravitreal, subretinal, and transscleral routes. Significantly smaller amounts of the components (compared with systemic approaches) may exert an effect when administered locally (for example, intraparenchymal or intravitreal) compared to when administered systemically (for example, intravenously). Local modes of administration may also reduce or eliminate the incidence of potentially toxic side effects that may occur when therapeutically effective amounts of a component are administered systemically. In a specific example, administration *in vivo* is intravenous.

[01380] Administration *in vivo* can be by any suitable route including, for example, parenteral, intravenous, oral, subcutaneous, intra-arterial, intracranial, intrathecal, intraperitoneal, intratumoral, topical, intranasal, or intramuscular. A specific example is intravenous infusion.

[01381] Administration *in vivo* can be by any suitable route including, for example, systemic routes of administration such as parenteral administration, e.g., intravenous, subcutaneous, intra-arterial, or intramuscular. In a specific example, administration *in vivo* is intravenous.

[01382] The frequency of administration and the number of dosages can depend on a number of factors. The introduction of an immunogen into the cell or subject can be performed one time

or multiple times over a period of time. For example, the introduction can be performed only once over a period of time, at least two times over a period of time, at least three times over a period of time, at least four times over a period of time, at least five times over a period of time, at least six times over a period of time, at least seven times over a period of time, at least eight times over a period of time, at least nine times over a period of times, at least ten times over a period of time, at least eleven times, at least twelve times over a period of time, at least thirteen times over a period of time, at least fourteen times over a period of time, at least fifteen times over a period of time, at least sixteen times over a period of time, at least seventeen times over a period of time, at least eighteen times over a period of time, at least nineteen times over a period of time, or at least twenty times over a period of time. In some methods, a single administration of the immunogen, e.g., a vector, is sufficient to increase expression of polypeptide of interest to a desirable level. In other methods, more than one administration may be beneficial to maximize therapeutic effect.

[01383] The methods disclosed herein can increase polypeptide of interest protein levels and/or polypeptide of interest activity levels in a cell or subject (e.g., circulating, serum, or plasma levels in a subject) and can comprise measuring polypeptide of interest protein levels and/or polypeptide of interest activity levels in a cell or subject (e.g., circulating, serum, or plasma levels in a subject).

[01384] In some methods, polypeptide of interest activity and/or expression levels in a subject are increased to about or at least about 2%, about or at least about 10%, about or at least about 25%, about or at least about 40%, about or at least about 50%, about or at least about 75%, or at least about 100%, or more, of normal level. In some methods, polypeptide of interest activity and/or expression levels in a subject are increased to about or at least about 40%, about or at least about 50%, about or at least about 75%, or at least about 100%, or more, of normal level.

[01385] In some methods, circulating polypeptide of interest levels (i.e., serum levels) are about or at least about 0.5, about or at least about 1, about or at least about 2, about or at least about 3, about or at least about 4, about or at least about 5, about or at least about 6, about or at least about 7, about or at least about 8, about or at least about 9, or about or at least about 10 μg/mL. In some methods, polypeptide of interest levels are at least about 1 μg/mL or about 1 μg/mL. In some methods, polypeptide of interest levels are at least about 2 μg/mL or about 2 μg/mL. In some methods, polypeptide of interest levels are at least about 5 μg/mL or about 5 μg/mL. In some methods, polypeptide of interest levels are about 1 μg/mL to about 30 μg/mL, about 2 μg/mL to about 30 μg/mL, about 3 μg/mL to about 30 μg/mL, about 4 μg/mL to about 30 μg/mL, about 5 μg/mL to about 30 μg/mL, about 1 μg/mL to about 20 μg/mL, about 2 μg/mL to about 20

μg/mL, about 3 μg/mL to about 20 μg/mL, about 4 μg/mL to about 20 μg/mL, about 5 μg/mL to about 20 μg/mL. For example, the method can result in polypeptide of interest levels of about 2 μg/mL to about 30 μg/mL or 2 μg/mL to about 20 μg/mL. For example, the method can result in polypeptide of interest levels of about 5 μg/mL to about 30 μg/mL or 5 μg/mL to about 20 μg/mL. In some embodiments, the recited expression levels are at least 1 month after administration. In some embodiments, the recited expression levels are at least 2 months after administration. In some embodiments, the recited expression levels are at least 3 months after administration. In some embodiments, the recited expression levels are at least 4 months after administration. In some embodiments, the recited expression levels are at least 5 months after administration. In some embodiments, the recited expression levels are at least 6 months after administration. In some embodiments, the recited expression levels are at least 9 months after administration. In some embodiments, the recited expression levels are at least 12 months after administration.

[01386] In some methods, the method increases expression and/or activity of polypeptide of interest over the subject's baseline expression and/or activity (i.e., expression and/or activity prior to administration). In some methods, the method increases expression and/or activity of polypeptide of interest over the subject's baseline expression and/or activity (i.e., expression and/or activity prior to administration. In some methods, polypeptide of interest activity and/or polypeptide of interest expression or serum levels in a subject are increased by about or at least about 10%, about or at least about 25%, about or at least about 50%, about or at least about 75%, or about or at least about 100%, or more, as compared to the subject's polypeptide of interest expression or serum levels and/or activity before administration (i.e., the subject's baseline levels). In certain embodiments, the loss of function is nearly complete such that a relative activity cannot be determined. In certain embodiments, the level of expression is sufficient to treat at least one sign or symptom resulting from the loss of function of the polypeptide of interest.

[01387] In some methods, the method increases expression and/or activity of the polypeptide of interest over the cell's baseline expression and/or activity (i.e., expression and/or activity prior to administration). In some methods, the method increases expression and/or activity of polypeptide of interest over the cell's baseline expression and/or activity (i.e., expression and/or activity prior to administration. In some methods, polypeptide of interest activity and/or expression levels in a cell or population of cells (e.g., liver cells, or hepatocytes) are increased by about or at least about 10%, about or at least about 25%, about or at least about 50%, about or at least about 75%, about or at least about 100%, or more, as compared to the polypeptide of interest activity and/or expression levels before administration (i.e., the subject's baseline

levels). In certain embodiments, the polypeptide of interest loss of function is nearly complete such that a relative activity cannot be determined. In certain embodiments, the level of expression is sufficient to treat at least one sign or symptom resulting from the loss of function of the polypeptide of interest.

[01388] In a specific example, the polypeptide of interest activity levels in a subject are increased to no more than about 300%, no more than about 250%, no more than about 200%, or no more than about 150% of normal polypeptide of interest activity levels.

[01389] In a specific example, the polypeptide of interest activity levels in the subject are increased to at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 100% of normal polypeptide of interest activity levels. In a specific example, the polypeptide of interest activity levels in the subject are increased to at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 100% of normal polypeptide of interest activity levels.

[01390] In some methods, the method results in increased expression of the polypeptide of interest in the subject (e.g., neonatal subject) compared to a method comprising administering an episomal expression vector encoding the polypeptide of interest in a control subject. In some methods, the method results in increased serum levels of the polypeptide of interest in the subject (e.g., neonatal subject) compared to a method comprising administering an episomal expression vector encoding the polypeptide of interest to a control subject.

[01391] In some methods, the method increases expression or activity of the polypeptide of interest over the subject's baseline expression or activity of the polypeptide of interest (i.e., any percent change in expression that is larger than typical error bars). In some methods, the method results in expression of the polypeptide of interest at a detectable level above zero, e.g., at a statistically significant level, a clinically relevant level.

[01392] In some methods, the expression or activity of the polypeptide of interest is at least 50% of the expression or activity of the polypeptide of interest at a peak level of expression measured for the subject at 24 weeks after the administering. In some methods, the expression or activity of the polypeptide of interest is at least 50% of the expression or activity of the polypeptide of interest at a peak level of expression measured for the subject at one year after

the administering. In some methods, the expression or activity of the polypeptide of interest is at least 60% of the expression or activity of the polypeptide of interest at a peak level of expression measured for the subject at 24 weeks after the administering. In some methods, the expression or activity of the polypeptide of interest is at least 50% of the expression or activity of the polypeptide of interest at a peak level of expression measured for the subject at two years after the administering. In some methods, the expression or activity of the polypeptide of interest is at least 60% of the expression or activity of the polypeptide of interest at a peak level of expression measured for the subject at 2 years after the administering. In some methods, the expression or activity of the polypeptide of interest is at least 60% of the expression or activity of the polypeptide of interest at a peak level of expression measured for the subject at 24 weeks after the administering.

[01393] In some methods, the method further comprises assessing preexisting anti-polypeptide of interest immunity in a subject prior to administering any of the nucleic acid constructs described herein. For example, such methods could comprise assessing immunogenicity using a total antibody (TAb) immune assay or a neutralizing antibody (NAb) assay. In some methods, the subject has not previously been administered recombinant polypeptide of interest protein. In some methods, the subject has previously been administered recombinant polypeptide of interest protein.

[01394] In some methods, the method further comprises assessing preexisting anti-AAV (e.g., anti-AAV8) immunity in a subject prior to administering any of the nucleic acid constructs described herein. For example, such methods could comprise assessing immunogenicity using a total antibody (TAb) immune assay or a neutralizing antibody (NAb) assay. *See, e.g.*, Manno et al. (2006) *Nat. Med.* 12(3):342-347, Kruzik et al. (2019) *Mol. Ther. Methods Clin. Dev.* 14:126-133, and Weber (2021) *Front. Immunol.* 12:658399, each of which is herein incorporated by reference in its entirety for all purposes. In some embodiments, TAb assays look for antibodies that bind to the AAV vector, whereas NAb assays assess whether the antibodies that are present stop the AAV vector from transducing target cells. With TAb assays, the drug product or an empty capsid can be used to capture the antibodies; NAb assays can require a reporter vector (e.g., a version of the AAV vector encoding luciferase). In some embodiments, the subject does not have preexisting anti-AAV immunity. In some embodiments, the subject does have preexisting AAV immunity.

[01395] In some embodiments of the methods for inhibiting or preventing an immune response to an immunogen described herein, the inhibiting of the immune response can comprise suppression of numbers and/or frequencies of plasma cells and/or B cells when the subject has

preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments of the methods for inhibiting or preventing an immune response to an immunogen described herein, the inhibiting of the immune response to the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can comprise suppression of the magnitude and/or duration of an immune response in a subject. In some embodiments, the immunogen is an immunogenic delivery vehicle, e.g., AAV. In some embodiments, the AAV is AAV8.

[01396] In some embodiments, the number and/or frequency of plasma cells and/or B cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The number and/or frequency of plasma cells and/or B cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The number and/or frequency of plasma cells and/or B cells may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01397] In some embodiments, the total number and/or frequency of plasma cells and/or B cells may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The total number and/or frequency of plasma cells and/or B cells may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The total number and/or frequency of plasma cells and/or B cells may be reduced

by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01398] In some embodiments, inhibiting the immune response comprises suppression of immunogen-specific IgG and/or IgM responses.

[01399] In some embodiments, the responses of IgG and/or IgM may be reduced by about 1%, about 2%, about 3%, about 4%, about 5%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The responses of IgG may be reduced by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The responses of IgG may be reduced by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%.

[01400] In some embodiments, the effectiveness of re-administration of an immunogen may be increased by about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7% about 8%, about 9%, about 10%, from about 10% to about 15%, from about 15% to about 20%, from about 20% to about 25%, from about 25% to about 30%, from about 30% to about 40%, from about 40% to about 50% or more. The effectiveness of re-administration of an immunogen be increased by from about 50% to about 60%, from about 50% to about 70%, from about 50% to about 80%, from about 50% to about 90%, more than 60%, from about 60% to about 70%, from about 60% to about 80%, from about 60% to about 90%, more than about 70%, from about 70% to about 80%, from about 70% to about 90%, more than about 80%, from about 80% to about 90%, more than 90%, from about 90% to about 95%, from about 90% to about 98%, more than 95%, from about 95% to about 98%, more than about 98%, or more than about 99%. The effectiveness of re-administration of an immunogen may be increased by about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99% or even 100%, or more.

Combination Therapies

[01401] The present disclosure includes compositions and therapeutic formulations comprising any of the exemplary antigen binding molecules, e.g., antibodies and bispecific antigen-binding molecules, CD40 inhibitors, and/or immunogens (e.g., immunogenic delivery vehicles) described herein in combination with one or more additional therapeutic agents, and methods of treatment comprising administering such combinations to subjects in need thereof. In some embodiments, the additional therapeutic agent(s) is an immunomodulatory agent. An immunomodulatory agent as disclosed herein can include, without limitation, a plasma cell depleting agent, a B cell depleting agent, or an immunoglobulin depleting agent, or any combination thereof. In some embodiments, the additional therapeutic agent(s) is an anti-inflammatory agent. In some embodiments, the additional therapeutic agent(s) is a therapeutic procedure. Such therapeutic procedure can comprise, without limitation, a plasma-based therapeutic procedure such as, but not limited to, plasmapheresis, therapeutic plasma exchange, or immunoadsorption, or any combination thereof. In some embodiments, the additional therapeutic agent(s) is immunosuppressive therapy. In some embodiments, the additional therapeutic agent(s) is a surgical procedure.

[01402] Exemplary additional therapeutic agents that may be combined with or administered in combination with an antigen-binding molecule, a CD40 inhibitor, and/or an immunogen of the present disclosure include, e.g., another CD40-CD40L inhibitor (e.g., an anti-CD40 antibody such as iscalimab [CFZ-533], ravagalimab [ABBV-323] /Ab102, BI-655064, bleselumab [ASKP1240], , ch5D12, lucatumumab [HCD122 or CHIR12.12], CHIR-5.9, abiprubart [KPL-404] PG102/FFP104, BIIB063, BMS3h-38, BMS3h-56, BMS3h-198,V19, V15, h2C10 and variants thereof , Ab101, Antibody A , Antibody B , Antibody C, G28.5, Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3], Y12XX-hz42 [Vh-hzl4;Vk-hz3] or teneliximab; or an anti-CD40L antibody or antigen-binding protein such as dapirolizumab pegol, dazodalibep [VIB4920], frexalimab [INX-021], letolizumab [BMS-986004], MR-1, ruplizumab [BG9588], tegoprubart [AT-1501], or toralizumab [IDEC-131].

[01403] Suitable combinations comprising a plasma cell depleting agent are described in more detail elsewhere herein. Such combinations can be further in combination with a CD40 inhibitor such as in the specific scenarios described herein. The plasma cell depleting agents or combinations comprising plasma cell depleting agents can inhibit or prevent an immune response to an immunogen (e.g., an immunogenic delivery vehicle) in a subject having preexisting immunity against the immunogen (i.e., an immunogen to be administered to the subject in need thereof) or can inhibit or prevent generation of antibodies (e.g., neutralizing

antibodies) to an immunogen (e.g., an immunogenic delivery vehicle) in a subject having preexisting immunity against the immunogen (i.e., an immunogen to be administered to the subject in need thereof).

[01404] Whenever administration of a plasma cell depleting agent, a B cell depleting agent, or an immunoglobulin depleting agent is discussed in this disclosure, it is in the context of being administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle). Likewise, whenever administration of a B cell depleting agent or an immunoglobulin depleting agent is discussed in this disclosure, it is in the context of being administered in combination with a plasma cell depleting agent.

[01405] An antibody may be capable of both binding and neutralizing an immunogen such as an immunogenic delivery vehicle, e.g., a viral particle, or a portion thereof (e.g., neutralizing antibody (nAb)). In some embodiments, the antibody may affect pharmacokinetic properties or alter uptake of, e.g., AAV into different cell types. In some embodiments, neutralizing (or neutralize or neutralization and the like) in the context of the present disclosure may comprise an effect of immunoglobulins, such as antibodies generated in a host immune response, in reducing the efficacy and/or delivery of, e.g., a viral particle. As an example, neutralization by an at least one nAb described herein may be realized such that the nAb is directed to, e.g., a viral particle surface (e.g., capsid protein) which may result in aggregation of viral particles and/or may be realized by inhibition of the fusion of viral and a cellular membrane(s) after attachment of the viral particle to a target cell, by inhibition of endocytosis, and/or by inhibition of production of viral progeny. In various embodiments, an antibody generated in a subject's host immune response can play a neutralizing role thereby causing the delivery effectiveness of the viral particle to be reduced or eliminated. In some embodiments, the induced and/or preexisting host immunity may comprise B and/or T cell immune responses described herein. The blockade and/or suppression of induced and/or preexisting host immunity against viral particles or portions thereof, can improve viral transduction and allow for effective re-administration (i.e., re-dosing) of the viral particles during gene therapy.

[01406] The additional therapeutically active component(s) may be administered just prior to, concurrent with, or shortly after the administration of an antigen-binding molecule of the present disclosure. For the purposes of the present disclosure, such administration regimens are considered the administration of an antigen-binding molecule "in combination with" an additional therapeutically active component.

[01407] The present disclosure includes pharmaceutical compositions in which an antigen-

binding molecule and/or a CD40 inhibitor and/or an immunogen (e.g., an immunogenic delivery vehicle) of the present invention is co-formulated with one or more of the additional therapeutically active component(s) as described elsewhere herein.

Exemplary Therapeutic Agents and Their Methods of Use

Plasma Cell Depleting Agents

[01408] In some embodiments, the compositions disclosed herein comprise or the methods disclosed herein include administering a therapeutically effective amount of a plasma cell depleting agent to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). As used herein, a "plasma cell depleting agent" refers to any molecule capable of specifically binding to a surface antigen on plasma cells and killing or depleting the plasma cells.

[01409] The plasma cell depleting agents can be administered to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) either alone or in combination with a B cell depleting agent and/or an immunoglobulin depleting agent. In various aspects, a plasma cell depleting agent may be combined or administered in combination with a B cell depleting agent, an immunoglobulin depleting agent, plasmapheresis, therapeutic plasma exchange, immunoadsorption, and/or an immunogen (e.g., in an immunogenic delivery vehicle such as, e.g., AAV) disclosed herein to a subject with preexisting immunity against the immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). Suitable combinations comprising a plasma cell depleting agent are described in more detail elsewhere herein. In some embodiments, the plasma cell depleting agent of the present disclosure is capable of depleting plasma cells including, without limitation, long-lived plasma cells (LLPCs). In some embodiments, a plasma cell depleting agent is administered to a subject having a pre-existing immunity against an immunogen (e.g. an immunogenic delivery vehicle such as, e.g., AAV).

[01410] In some embodiments, the plasma cell depleting agent can be an antibody, a small molecule compound, a nucleic acid, a polypeptide, or a functional fragment or variant thereof. Non-limiting examples of suitable plasma cell depleting agents include B cell maturation antigen (BCMA) targeting agents (described elsewhere herein), proteasome inhibitors [e.g., bortezomib (Velcade), carfilzomib (Kyprolis), ixazomib (Niniaro)], histone deacetylase inhibitors [e.g., panobinostat (Farydak)], B-cell activating factor (BAFF; also referred to as BLyS, TALL-1, or

CD257) inhibitors (e.g., anti-BAFF antibodies such as belimumab, tabalumab, AMG570; or anti-BAFF receptor antibodies such as ianalumab), proliferation-inducing ligand (APRIL; also referred to as TNFSF13 or CD256) inhibitors (e.g., anti-APRIL antibodies such as BION-1301 or VIS624), G protein–coupled receptor, class C, group 5, member D (GPRC5D) inhibitors (e.g., anti-GPRC5D antibodies, anti-GPRC5DxCD3 bispecific antibodies such as talquetamab), Fc receptor homolog 5 (FcRH5; also referred to as FcRL5, IRTA2, or CD307) inhibitors (e.g., anti-FcRH5 antibodies, anti-FcRH5 xCD3 bispecific antibodies such as Cevostamab), and cluster of differentiation 38 (CD38; also referred to as CADPR1 or ADPRC1) inhibitors (e.g., anti-CD38 antibodies).

[01411] In some embodiments, the plasma cell depleting agents used in the compositions and methods disclosed herein are BCMA targeting agents. As used herein, the term "BCMA targeting agent" refers to any molecule capable of binding specifically to BCMA that is expressed on the surface of a cell, e.g., a cell in a subject, thus targeting the cell for destruction. BCMA is expressed exclusively in B-cell lineage cells, particularly in the interfollicular region of the germinal center, as well as on plasmablasts and differentiated plasma cells. BCMA is selectively induced during plasma cell differentiation and is required for optimal survival of long-lived plasma cells (LLPCs) in the bone marrow. Thus, a BCMA targeting agent binds to BCMA expressed on a plasma cell surface and mediates killing or depletion of cells that express BCMA (plasma cell depletion). In some embodiments, a BCMA targeting agent comprises a binding moiety that binds to plasma cell-surface-expressed BCMA (an antigen-binding moiety or antigen-binding fragment thereof) and a moiety that facilitates killing of said plasma cell. In some embodiments, the plasma cell-surface-expressed BCMA-binding moiety is an antibody or antigen-binding fragment thereof that binds specifically to BCMA. Such a BCMA-binding moiety can be linked (e.g., covalently bound) to a moiety that facilitates killing or destruction of the targeted plasma cell. The moiety that facilitates targeted killing of the bound plasma cell may be a molecule that directly kills the targeted cell (e.g., a cytotoxic agent) or may be a protein or fragment thereof that mediates killing of the targeted cell, e.g., by an immune cell, e.g., a T-cell. In the context of the present disclosure, the term "BCMA targeting agent" includes, but is not limited to, anti-BCMA antibodies that are conjugated to a therapeutic agent such as a cytotoxic drug ("BCMA ADC" or "anti-BCMA ADC," e.g., Belantamab Mafodotin / GSK2857916, MEDI2228, HDP-101), chimeric antigenic receptors (CARs) that bind specifically to BCMA, ("BCMA CAR" or "anti-BCMA CAR") and anti-BCMAxCD3 bispecific antibodies (e.g., linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135),

TNB383B (ABBV-383), and TNB384B).

[01412] In some embodiments, the BCMA targeting agent used in the context of the disclosed methods is an antibody-drug conjugate (ADC) comprising an anti-BCMA antibody and a cytotoxic drug. In some embodiments, the anti-BCMA antibody or antigen-binding fragment thereof and the cytotoxic agent are covalently attached via a linker. In general terms, the ADCs comprise: A-[L-P]y, in which A is an antigen-binding molecule, e.g., an anti-BCMA antibody, or a fragment thereof, L is a linker, P is the payload or therapeutic moiety (e.g., cytotoxic agent), and y is an integer from 1 to 30. Examples of suitable cytotoxic agents and chemotherapeutic agents for forming ADCs are known in the art. Non-limiting examples of suitable cytotoxic agents that can be conjugated to anti-BCMA antibodies for use in the disclosed methods are auristatin such as monomethyl auristatin E (MMAE) or monomethyl auristatin F (MMAF), a tubulysin such as TUB-OH or TUB-OMOM, a tomaymycin derivative, a dolastatin derivative, or a maytansinoid such as DM1 or DM4. In some exemplary embodiments, an anti-BCMA ADC used in the present methods comprises the HCVR, LCVR, and/or CDR amino acid sequences of any of the anti-BCMA antigen-binding molecules disclosed herein.

[01413] Other anti-BCMA ADCs that can be used in the context of the methods of the present disclosure include, e.g., the ADCs referred to and known in the art as Belantamab Mafodotin (GSK2857916), AMG224, HDP-101, MEDI2228, and TBL-CLN1, or any of the anti-BCMA ADCs set forth, e.g., in International Patent Publications WO2011/108008, WO2014/089335, WO2017/093942, WO2017/143069, or WO2019/025983. The portions of the publications cited herein that identify anti-BCMA ADCs are hereby incorporated by reference.

[01414] In some embodiments, the BCMA targeting agent used in the context of the disclosed methods is a chimeric antigen receptor (CAR) that binds specifically to BCMA ("BCMA CAR"). Generally, a "chimeric antigen receptor" (CAR) exhibits a specific anti-target cellular immune activity and comprises a binding domain against a component present on the target cell, for example an antibody-based specificity for a desired antigen (e.g., BCMA on plasma cell), and a T cell receptor-activating intracellular domain. CARs typically comprise an extracellular single chain antibody-binding domain (scFv) fused to the intracellular signaling domain of the T cell antigen receptor complex zeta chain, and have the ability, when expressed in T cells, to redirect antigen recognition based on the monoclonal antibody's specificity. In certain embodiments, the BCMA CAR or antigen-binding fragment thereof comprises a HCVR, LCVR, and/or CDRs comprising the amino acid sequences of any of the antibodies set forth in US Patent Publication No. US 2020/0023010, which is hereby incorporated by reference in its entirety. In some exemplary embodiments, an anti-BCMA CAR used in the present methods comprises the

HCVR, LCVR, and/or CDR amino acid sequences of any of the anti-BCMA antigen-binding molecules disclosed herein.

[01415] Other anti-BCMA CARs that can be used in the context of the methods of the present disclosure include, e.g., the CARs referred to and known in the art as bb2121, LCAR-B38M, and 4C8A, or any of the anti-BCMA CARs set forth, e.g., in WO 2015/052538, WO 2015/052536, WO 2016/094304, WO 2016/166630, WO 2016/151315, WO 2016/130598, WO 2017/183418, WO 2017/173256, WO 2017211900, WO 2017/130223, WO 2018/229492, WO 2018/085690, WO 2018/151836, WO 2018/028647, WO 2019/006072. The portions of the publications cited herein that identify anti-BCMA CARs are hereby incorporated by reference.

[01416] In some exemplary embodiments, the BCMA targeting agent used in the disclosed methods is a multispecific (e.g., bispecific) antibody, or a functional fragment thereof, that specifically binds B cell maturation antigen (BCMA) and CD3 (e.g., an anti-BCMA×CD3 bispecific antibody). The anti-BCMAxCD3 multispecific (e.g., bispecific) antibodies are useful for specific targeting and T-cell-mediated killing of cells that express BCMA. The terms "antibody," "antigen-binding fragment," "human antibody," "recombinant antibody," and other related terminology are defined above. In the context of anti-BCMAxCD3 antibodies and antigen-binding fragments thereof, the present disclosure includes the use of bispecific antibodies wherein one arm of an immunoglobulin is specific for BCMA or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target (e.g., CD3 on T-cells). Exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, e.g., scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (e.g., common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED) body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mabe bispecific formats (see, e.g., Klein et al. 2012, mAbs 4(6):653-663, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, e.g., wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. See, e.g., Kazane et al., J. Am. Chem. Soc., 2013, 135(1):340-46.

[01417] An anti-BCMAxCD3 bispecific antibody, or functional fragment thereof, may comprise any of various anti-BCMAxCD3 bispecific antibodies, or functional fragments thereof, disclosed herein, or any other such anti-BCMAxCD3 bispecific antibodies, or functional fragments thereof, known to persons of ordinary skill in the art (e.g., linvoseltamab (REGN5458), REGN5459,

pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B). In a specific embodiment, the anti-BCMAxCD3 bispecific antibody is REGN5458. In another specific embodiment, the anti-BCMAxCD3 bispecific antibody is REGN5459.

CD3 Antigen-Binding Molecules

[01418] The term "CD3," as used herein, refers to an antigen which is expressed on T cells as part of the multimolecular T cell receptor (TCR) and which consists of a homodimer or heterodimer formed from the dimeric association of two of four receptor chains: CD3-epsilon, CD3-delta, CD3-zeta, and CD3-gamma (e.g., gamma/epsilon, delta/epsilon, and zeta/zeta). CD3 is required for T cell activation.

[01419] As used herein, "an antibody that binds CD3" or an "anti-CD3 antibody" includes antibodies and antigen-binding fragments thereof that specifically recognize a single CD3 subunit (e.g., epsilon, delta, gamma or zeta), as well as antibodies and antigen-binding fragments thereof that specifically recognize a dimeric complex of two CD3 subunits (e.g., gamma/epsilon, delta/epsilon, and zeta/zeta CD3 dimers). Antibodies against CD3 have been shown to cluster CD3 on T cells, thereby causing T cell activation in a manner similar to the engagement of the TCR by peptide-loaded major histocompatibility complex (MHC) molecules. Thus, bispecific antigen-binding molecules that are capable of binding both CD3 and another antigen (e.g., CD20 or BCMA) would be useful in settings in which specific targeting and T cell-mediated killing of cells that express the non-CD3 antigen (e.g., CD20 or BCMA) is desired.

[01420] The antibodies and antigen-binding fragments of the present invention may bind soluble CD3 and/or cell surface-expressed CD3. Soluble CD3 includes natural CD3 proteins as well as recombinant CD3 protein variants such as, e.g., monomeric and dimeric CD3 constructs, that lack a transmembrane domain or are otherwise unassociated with a cell membrane.

[01421] As used herein, the expression "cell surface-expressed CD3" means one or more CD3 protein(s) that is/are expressed on the surface of a cell *in vitro* or *in vivo*, such that at least a portion of a CD3 protein is exposed to the extracellular side of the cell membrane and is accessible to an antigen-binding portion of an antibody. "Cell surface-expressed CD3" includes CD3 proteins contained within the context of a functional T cell receptor in the membrane of a cell. The expression "cell surface-expressed CD3" includes CD3 protein expressed as part of a homodimer or heterodimer on the surface of a cell (e.g., gamma/epsilon, delta/epsilon, and zeta/zeta CD3 dimers). The expression "cell surface-expressed CD3" also includes a CD3 chain (e.g., CD3-epsilon, CD3-delta or CD3-gamma) that is expressed by itself, without other CD3 chain types, on the surface of a cell. A "cell surface-expressed CD3" can comprise or consist of

a CD3 protein expressed on the surface of a cell which normally expresses CD3 protein. Alternatively, "cell surface-expressed CD3" can comprise or consist of CD3 protein expressed on the surface of a cell that normally does not express human CD3 on its surface but has been artificially engineered to express CD3 on its surface.

[01422] As used herein, the expression "anti-CD3 antibody" includes both monovalent antibodies with a single specificity, as well as bispecific antibodies comprising one arm that binds CD3 and another arm that binds a different antigen, wherein the anti-CD3 arm comprises any of the HCVR/LCVR or CDR sequences, or functional fragments thereof, as set forth in Table 1 or Table 2 herein. Examples of anti-CD3 bispecific antibodies are described elsewhere herein. Exemplary anti-CD3 antibodies are also described in PCT International Application No. PCT/US2013/060511, which is herein incorporated by reference in its entirety.

[01423] The present disclosure includes bispecific antibodies and functional fragments thereof that bind human CD3 with high affinity. The present disclosure also includes bispecific antibodies and functional fragments thereof that bind human CD3 with medium or low affinity, depending on the therapeutic context and particular targeting properties that are desired. For example, in the context of a bispecific antigen-binding molecule, wherein one arm binds CD3 and a second arm binds another antigen (e.g., CD20 or BCMA), it may be desirable for the second arm to bind the non-CD3 (e.g., CD20 or BCMA) antigen with high affinity while the anti-CD3 arm binds CD3 with only moderate or low affinity. In this manner, preferential targeting of the antigen-binding molecule to cells expressing the non-CD3 (e.g., CD20 or BCMA) antigen may be achieved while avoiding general/untargeted CD3 binding and the consequent adverse side effects associated therewith.

[01424] In certain embodiments, the anti-CD3 antibodies induce T cell proliferation with an EC_{50} value of less than about 0.33 pM, as measured by an *in vitro* T cell proliferation assay (e.g., assessing the proliferation of Jurkat cells or PBMCs in the presence of anti-CD3 antibodies). In certain embodiments, the anti-CD3 antibodies induce T cell proliferation (e.g., Jurkat cell proliferation and/or PBMC proliferation) with an EC_{50} value of less than about 0.32 pM, less than about 0.31 pM, less than about 0.30 pM, less than about 0.28 pM, less than about 0.26 pM, less than about 0.24 pM, less than about 0.22 pM, or less than about 0.20 pM, as measured by an *in vitro* T cell proliferation assay.

BCMAxCD3 Antigen-Binding Molecules

[01425] In some embodiments, the present disclosure provides antigen-binding molecules including multispecific (e.g., bispecific) antibodies that specifically bind B cell maturation antigen (BCMA) and CD3 (e.g., an anti-BCMAxCD3 bispecific antibody). In some embodiments, the

antigen-binding molecule is a multispecific (e.g., bispecific) antibody. Multispecific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., 1991, J. Immunol. 147:60-69; Kufer et al., 2004, Trends Biotechnol. 22:238-244. In some embodiments, the multispecific antibodies of the present disclosure can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment, to produce a bispecific or a multispecific antibody with a second binding specificity. In some embodiments, the multispecific antibody contains an antigen-binding domain that is specific for BCMA and an antigen-binding domain that is specific for CD3.

[01426] In some embodiments, the anti-BCMAxCD3 bispecific antigen-binding molecule comprises a first antigen-binding domain (D1) that binds an epitope of BCMA (e.g., human BCMA), and a second antigen-binding domain (D2) that binds an epitope of CD3 (e.g., human CD3).

[01427] In some exemplary embodiments, the anti-BCMAxCD3 bispecific antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising the amino acid sequences of any of the anti-BCMAxCD3 antibodies set forth in US 11,384,153 and US 2020/0345843, which are hereby incorporated by reference in their entireties.

[01428] In some exemplary embodiments, an anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof that can be used in the context of the present disclosure comprising a HCVR, a LCVR, and/or CDRs comprising the amino acid sequences of REGN5458 or REGN5459 as set forth in **Table 1** below.

Table 1. Amino Acid Sequences of Exemplary Anti-BCMA×CD3 Bispecific Antibodies.

	Anti-BCMA First Antigen-Binding Domain				**Anti-CD3 Second Antigen-Binding Domain**				**Common Light Chain Variable Region**			
Bispecific antibody identifier	HCVR	HCDR1	HCDR2	HCDR3	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
REGN5458	1055	1057	1059	1061	1079	1081	1083	1085	1071	1073	1075	1077
REGN5459	1055	1057	1059	1061	1087	1089	1091	1093	1071	1073	1075	1077

SEQ ID NO: 1054 Anti-BCMA HCVR DNA Sequence

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGG
ATTCACCTTTAGTAACTTTTGGATGACCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATGA
ACCAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAGC
TCACTGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCGGGAATATTG
TATTAGTACCAGCTGCTATGATGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA

SEQ ID NO: 1055 - Anti-BCMA HCVR Protein Sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFWMTWVRQAPGKGLEWVANMNQDGSEKYYVDSVKGRFTISRDNAKS
SLYLQMNSLRAEDTAVYYCARDREYCISTSCYDDFDYWGQGTLVTVSS

SEQ ID NO: 1056 - Anti-BCMA HCDR1 DNA Sequence

GGATTCACCTTTAGTAACTTTTGG

SEQ ID NO: 1057 - Anti-BCMA HCDR1 Protein Sequence

GFTFSNFW

SEQ ID NO: 1058 - Anti-BCMA HCDR2 DNA Sequence

ATGAACCAAGATGGAAGTGAGAAA

SEQ ID NO: 1059 - Anti-BCMA HCDR2 Protein Sequence

MNQDGSEK

SEQ ID NO: 1060 - Anti-BCMA HCDR3 DNA Sequence

GCGAGAGATCGGGAATATTGTATTAGTACCAGCTGCTATGATGACTTTGACTAC

SEQ ID NO: 1061 - Anti-BCMA HCDR3 Protein Sequence

ARDREYCISTSCYDDFDY

SEQ ID NO: 1062 - Anti-BCMA LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAG
TCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCAT
CCAGTTTGCATAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGT
CTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGAC
ACGACTGGAGATTAAA

SEQ ID NO: 1063- Anti-BCMA LCVR Protein Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLHSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQSYSTPPITFGQGTRLEIK

SEQ ID NO: 1064- Anti-BCMA LCDR1 DNA Sequence

CAGAGCATTAGCAGCTAT

SEQ ID NO: 1065- Anti-BCMA LCDR1 Protein Sequence

QSISSY

SEQ ID NO: 1066- Anti-BCMA LCDR2 DNA Sequence

GCTGCATCC

SEQ ID NO: 1067- Anti-BCMA LCDR2 Protein Sequence

AAS

SEQ ID NO: 1068- Anti-BCMA LCDR3 DNA Sequence

CAACAGAGTTACAGTACCCCTCCGATCACC

SEQ ID NO: 1069- Anti-BCMA LCDR3 Protein Sequence

QQSYSTPPIT

SEQ ID NO: 1070- Common LCVR DNA Sequence

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAG
TCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCAT
CCAGTTTGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGT
CTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGAC
ACGACTGGAGATTAAA

SEQ ID NO: 1071- Common LCVR Protein Sequence

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQSYSTPPITFGQGTRLEIK

SEQ ID NO: 1072- Common LCDR1 DNA Sequence

CAGAGCATTAGCAGCTAT

SEQ ID NO: 1073- Common LCDR1 Protein Sequence

QSISSY

SEQ ID NO: 1074- Common LCDR2 DNA Sequence

GCTGCATCC

SEQ ID NO: 1075- Common LCDR2 Protein sequence

AAS

SEQ ID NO: 1076- Common LCDR3 DNA sequence

CAACAGAGTTACAGTACCCCTCCGATCACC

SEQ ID NO: 1077- Common LCDR3 Protein Sequence

QQSYSTPPIT

SEQ ID NO: 1078- Anti-CD3 HCVR DNA Sequence – REGN5458

GAAGTACAGCTTGTAGAATCCGGCGGAGGACTGGTACAACCTGGAAGAAGTCTTAGACTGAGTTGCGCAGCTAGTGG
GTTTACATTCGACGATTACAGCATGCATTGGGTGAGGCAAGCTCCTGGTAAAGGATTGGAATGGGTTAGCGGGATAT
CATGGAACTCAGGAAGCAAGGGATACGCCGACAGCGTGAAAGGCCGATTTACAATATCTAGGGACAACGCAAAAAAC
TCTCTCTACCTTCAAATGAACTCTCTTAGGGCAGAAGACACAGCATTGTATTATTGCGCAAAATACGGCAGTGGTTA
TGGCAAGTTTTATCATTATGGACTGGACGTGTGGGGACAAGGGACAACAGTGACAGTGAGTAGC

SEQ ID NO: 1079- Anti-CD3 HCVR Protein Sequence – REGN5458

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADSVKGRFTISRDNAKN
SLYLQMNSLRAEDTALYYCAKYGSGYGKFYHYGLDVWGQGTTVTVSS

SEQ ID NO: 1080- Anti-CD3 HCDR1 DNA Sequence – REGN5458

GGGTTTACATTCGACGATTACAGC

SEQ ID NO: 1081- Anti-CD3 HCDR1 Protein Sequence – REGN5458

GFTFDDYS

SEQ ID NO: 1082- Anti-CD3 HCDR2 DNA Sequence – REGN5458

ATATCATGGAACTCAGGAAGCAAG

SEQ ID NO: 1083- Anti-CD3 HCDR2 Protein Sequence – REGN5458

ISWNSGSK

SEQ ID NO: 1084- Anti-CD3 HCDR3 DNA Sequence – REGN5458

GCAAAATACGGCAGTGGTTATGGCAAGTTTTATCATTATGGACTGGACGTG

SEQ ID NO: 1085- Anti-CD3 HCDR3 Protein Sequence – REGN5458

AKYGSGYGKFYHYGLDV

SEQ ID NO: 1086- Anti-CD3 HCVR DNA Sequence – REGN5459

GAAGTACAGCTTGTAGAATCCGGCGGAGGACTGGTACAACCTGGAAGAAGTCTTAGACTGAGTTGCGCAGCTAGTGG
GTTTACATTCGACGATTACAGCATGCATTGGGTGAGGCAAGCTCCTGGTAAAGGATTGGAATGGGTTAGCGGGATAT
CATGGAACTCAGGAAGCATCGGATACGCCGACAGCGTGAAAGGCCGATTTACAATATCTAGGGACAACGCAAAAAAC
TCTCTCTACCTTCAAATGAACTCTCTTAGGGCAGAAGACACAGCATTGTATTATTGCGCAAAATACGGCAGTGGTTA
TGGCAAGTTTTATTATTATGGAATGGACGTGTGGGGACAAGGGACAACAGTGACAGTGAGTAGC

SEQ ID NO: 1087- Anti-CD3 HCVR Protein Sequence – REGN5459

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKN
SLYLQMNSLRAEDTALYYCAKYGSGYGKFYYYGMDVWGQGTTVTVSS

SEQ ID NO: 1088- Anti-CD3 HCDR1 DNA Sequence – REGN5459

GGGTTTACATTCGACGATTACAGC

SEQ ID NO: 1089- Anti-CD3 HCDR1 Protein Sequence – REGN5459

GFTFDDYS

SEQ ID NO: 1090- Anti-CD3 HCDR2 DNA Sequence – REGN5459

ATATCATGGAACTCAGGAAGCATC

SEQ ID NO: 1091- Anti-CD3 HCDR2 Protein Sequence – REGN5459

ISWNSGSI

SEQ ID NO: 1092- Anti-CD3 HCDR3 DNA Sequence – REGN5459

GCAAAATACGGCAGTGGTTATGGCAAGTTTTATTATTATGGAATGGACGTG

SEQ ID NO: 1093- Anti-CD3 HCDR3 Protein Sequence – REGN5459

AKYGSGYGKFYYYGMDV

SEQ ID NO: 1094- Anti-BCMA Heavy Chain Protein Sequence (IgG4 Heavy Chain Constant Region)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFWMTWVRQAPGKGLEWVANMNQDGSEKYYVDSVKGRFTISRDNAKS
SLYLQMNSLRAEDTAVYYCARDREYCISTSCYDDFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPC

PPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

SEQ ID NO: 1095- Anti-CD3 Heavy Chain Protein Sequence (IgG4 Heavy Chain Constant Region with H435R/Y436F)

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADSVKGRFTISRDNAKN
SLYLQMNSLRAEDTALYYCAKYGSGYGKFYHYGLDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCP
PCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWE
SNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNRFTQKSLSLSPGK

SEQ ID NO: 1096– Common Anti-BCMA and Anti-CD3 Light Chain Protein Sequence (Kappa Light Chain Constant Region)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISS
LQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNA
LQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

[01429] In some embodiments, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof that can be used in the present disclosure comprises: (a) a first antigen binding domain that binds specifically to BCMA; and (b) a second antigen-binding domain that binds specifically to CD3. In one embodiment, the anti-BCMA antigen-binding domain comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071. In one embodiment, the first antigen-binding domain comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 1057; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 1059; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 1061; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 1073; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 1075; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 1077. In one embodiment, the second antigen-binding domain comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino

acid sequence of SEQ ID NO: 1079 or 1087 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071. In one embodiment, the second antigen-binding domain comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 1081 or 1089; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 1083 or 1091; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 1085 or 1093; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 1073; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 1075; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 1077.

[01430] In one embodiment, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, and LCDR1, LCDR2, and LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077; and (b) a second antigen binding domain that comprises HCDR1, HCDR2, and HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, and LCDR1, LCDR2, and LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077. In one embodiment, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1055 and a LCVR comprising the amino acid sequence of SEQ ID NO: 1071; and (b) a second antigen-binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1079 and a LCVR comprising the amino acid sequence of SEQ ID NO: 1071.

[01431] In one embodiment, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, and LCDR1, LCDR2, and LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077; and (b) a second antigen binding domain that comprises HCDR1, HCDR2, and HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, and LCDR1, LCDR2, and LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077. In one embodiment, the anti-BCMA/anti-CD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1055 and a LCVR comprising the amino

acid sequence of SEQ ID NO: 1071; and (b) a second antigen-binding domain that comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1087 and a LCVR comprising the amino acid sequence of SEQ ID NO: 1071.

[01432] Exemplary anti-BCMAxCD3 bispecific antibodies include the fully human bispecific antibodies known as REGN5458 and REGN5459. See, e.g., WO 2020/018820, US 2020/0024356, US 2022/0306758, and US 11,384,153, each of which is herein incorporated by reference. According to certain exemplary embodiments, the methods of the present disclosure comprise the use of REGN5458 or REGN5459, or a bioequivalent thereof. As used herein, the term "bioequivalent" with respect to anti-BCMAxCD3 antibodies refers to antibodies or BCMAxCD3 binding proteins or fragments thereof that are pharmaceutical equivalents or pharmaceutical alternatives having a rate and/or extent of absorption that does not show a significant difference with that of a reference antibody (e.g., REGN5458 or REGN5459) when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose; the term "bioequivalent" also includes antigen-binding proteins that bind to BCMA/CD3 and do not have clinically meaningful differences with the reference antibody (e.g., REGN5458 or REGN5459) with respect to safety, purity, and/or potency.

[01433] In some embodiments, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1055 and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071; and (b) a second antigen-binding domain that comprises a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1079 and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071. In some embodiments, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1055, and comprises three LCDRs (LCDR1, LCDR2 and LCDR3) comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively, and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071; and (b) a second antigen-binding domain that comprises three HCDRs

(HCDR1, HCDR2 and HCDR3) comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1079, and comprises three LCDRs (LCDR1, LCDR2 and LCDR3) comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively, and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071.

[01434] In some embodiments, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1055 and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071; and (b) a second antigen-binding domain that comprises a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1087 and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071. In some embodiments, the anti-BCMAxCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1055, and comprises three LCDRs (LCDR1, LCDR2 and LCDR3) comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively, and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071; and (b) a second antigen-binding domain that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and a HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1087, and comprises three LCDRs (LCDR1, LCDR2 and LCDR3) comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively, and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1071.

[01435] The present disclosure also includes variants of the anti-BCMAxCD3 antibodies described herein comprising any of the HCVR, LCVR, and/or CDR amino acid sequences

disclosed herein with one or more conservative amino acid substitutions. For example, the present disclosure includes use of anti-BCMAxCD3 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. In some embodiments, the disclosure includes use of an anti-BCMAxCD3 antibody having HCVR, LCVR, and/or CDR amino acid sequences with 1, 2, 3, or 4 conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[01436] Other anti-BCMAxCD3 antibodies that can be used in the methods of the present disclosure include, e.g., the antibodies referred to and known in the art as pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B, or any of the anti-BCMAxCD3 antibodies set forth, e.g., in WO 2013/072415, WO 2014/140248, WO 2014/122144, WO 2016/166629, WO 2016/079177, WO 2016/020332, WO 2017/031104, WO 2017/223111, WO 2017/134134, WO 2018/083204, or WO 2018/201051. The portions of the publications cited herein that identify anti-BCMAxCD3 antibodies are hereby incorporated by reference.

[01437] In some embodiments, the CDRs disclosed herein are identified according to the Kabat definition. In some embodiments, the CDRs are identified according to the Chothia definition. In some embodiments, the CDRs are identified according to the AbM definition. In some embodiments, the CDRs are identified according to the IMGT definition.

[01438] The bispecific antigen-binding molecules disclosed herein may be bispecific antibodies. In some cases, the bispecific antibody comprises a human IgG heavy chain constant region. In some cases, the human IgG heavy chain constant region is isotype IgG1. In some cases, the human IgG heavy chain constant region is isotype IgG4.

[01439] In some embodiments, the heavy chain constant region attached to the HCVR of the first antigen-binding domain or the heavy chain constant region attached to the HCVR of the second antigen-binding domain, but not both, contains an amino acid modification that reduces Protein A binding relative to a heavy chain of the same isotype without the modification. In some cases, the modification comprises a H435R substitution (EU numbering) in a heavy chain of isotype IgG1 or IgG4. In some cases, the modification comprises a H435R substitution and a Y436F substitution (EU numbering) in a heavy chain of isotype IgG1 or IgG4.

[01440] In some embodiments, the antibody comprises a first heavy chain containing the HCVR of the first antigen-binding domain and a second heavy chain containing the HCVR of the

second antigen-binding domain, wherein the first heavy chain comprises residues 1-450 of the amino acid sequence of SEQ ID NO: 1094 and the second heavy chain comprises residues 1-449 of the amino acid sequence of SEQ ID NO: 1095.

[01441] In some embodiments, the antibody comprises a common light chain containing the LCVR of the first and second antigen-binding domains, wherein the common light chain comprises the amino acid sequence of SEQ ID NO: 1096.

[01442] In some embodiments, the anti-BCMAxCD3 bispecific antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 1094, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 1095, and a common light chain comprising the amino acid sequence of SEQ ID NO: 1096. In some cases, the mature form of the antibody may not include the C-terminal lysine residues of SEQ ID NOs: 1094 and 1095. Thus, in some cases the anti-BCMA binding arm comprises a heavy chain comprising residues 1-450 of SEQ ID NO: 1094, and the anti-CD3 binding arm comprises a heavy chain comprising residues 1-449 of SEQ ID NO: 1095.

[01443] The first antigen-binding domain and the second antigen-binding domain may be directly or indirectly connected to one another to form a bispecific antigen-binding molecule. Alternatively, the first antigen-binding domain and the second antigen-binding domain may each be connected to a separate multimerizing domain. The association of one multimerizing domain with another multimerizing domain facilitates the association between the two antigen-binding domains, thereby forming a bispecific antigen-binding molecule. As used herein, a "multimerizing domain" is any macromolecule, protein, polypeptide, peptide, or amino acid that has the ability to associate with a second multimerizing domain of the same or similar structure or constitution. For example, a multimerizing domain may be a polypeptide comprising an immunoglobulin CH3 domain. A non-limiting example of a multimerizing component is an Fc portion of an immunoglobulin (comprising a CH2-CH3 domain), e.g., an Fc domain of an IgG selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group.

[01444] In some embodiments, a bispecific antigen-binding molecule of the present disclosure comprises two multimerizing domains, e.g., two Fc domains that are each individually part of a separate antibody heavy chain. The first and second multimerizing domains may be of the same IgG isotype such as, e.g., IgG1/IgG1, IgG2/IgG2, IgG4/IgG4. Alternatively, the first and second multimerizing domains may be of different IgG isotypes such as, e.g., IgG1/IgG2, IgG1/IgG4, IgG2/IgG4, etc.

[01445] In some embodiments, the multimerizing domain is an Fc fragment or an amino acid

sequence of from 1 to about 200 amino acids in length, containing at least one cysteine residue. In other embodiments, the multimerizing domain is a cysteine residue, or a short cysteine-containing peptide. Other multimerizing domains include peptides or polypeptides comprising or consisting of a leucine zipper, a helix-loop motif, or a coiled-coil motif.

Sequence Variants

[01446] The antigen-binding molecules of the present disclosure may comprise one or more amino acid substitutions, insertions, and/or deletions in the framework and/or CDR regions of the heavy and/or light chain variable domains as compared to the corresponding germline sequences from which the individual antigen-binding domains were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germ line sequences available from, for example, public antibody sequence databases. The antigen-binding molecules of the present disclosure may comprise antigen binding fragments which are derived from any of the exemplary amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as “germline mutations”). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the VH and/or VL domains are mutated back to the residues found in the original germline sequence from which the antigen-binding domain was originally derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germ line sequence from which the antigen-binding domain was originally derived). Furthermore, the antigen-binding domains may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germ line sequence while certain other residues that differ from the original germ line sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained,

antigen-binding domains that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved, or enhanced antagonistic or agonistic biological properties, reduced immunogenicity, etc. Bispecific antigen-binding molecules comprising one or more antigen-binding domains obtained in this general manner are encompassed within the present disclosure.

[01447] The present disclosure also includes antigen-binding molecules wherein one or both antigen-binding domains comprise variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present disclosure includes antigen-binding molecules comprising an antigen-binding domain having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 9 or fewer, 8 or fewer, 7 or fewer, 6 or fewer, 5 or fewer, 4 or fewer, 3 or fewer, 2 or fewer, or 1 conservative amino acid substitution(s) relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. In some embodiments, the disclosure includes use of an antibody having HCVR, LCVR, and/or CDR amino acid sequences with 1, 2, 3, or 4 conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. Examples of groups of amino acids that have side chains with similar chemical properties include (1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; (2) aliphatic-hydroxyl side chains: serine and threonine; (3) amide-containing side chains: asparagine and glutamine; (4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; (5) basic side chains: lysine, arginine, and histidine; (6) acidic side chains: aspartate and glutamate; and (7) sulfur-containing side chains are cysteine and methionine. Preferred conservative amino acids substitution groups are valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) Science 256: 1443-1445. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[01448] The present disclosure also includes antigen-binding molecules comprising an antigen binding domain with a HCVR, LCVR, and/or CDR amino acid sequence that is substantially identical to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. In some embodiments, an antigen-binding molecule comprises a HCVR, LCVR, and/or CDR

amino acid sequence having at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to a sequence disclosed in **Table 1**. In some embodiments, an antigen-binding molecule comprises a HCVR, LCVR, and/or CDR amino acid sequence having at least 85% sequence identity, e.g., at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to a sequence disclosed in **Table 1**, wherein the differences in the amino acid residue(s) relative to the sequence disclosed in **Table 1** are conservative substitutions or moderately conservative substitutions.

Antigen-Binding Proteins Comprising Fc Modifications

[01449] In some embodiments, an antigen-binding molecule as disclosed herein (e.g., a BCMAxCD3 bispecific antigen-binding molecule such as an anti-BCMAxCD3 bispecific antibody or a CD20xCD3 bispecific antigen-binding molecule such as an anti-CD20xCD3 bispecific antibody) comprises an Fc domain comprising one or more modifications or mutations that enhance or diminish antibody binding to the FcRn receptor. For example, the present disclosure includes antigen-binding molecules comprising one or more mutations in the CH2 and/or CH3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal.

[01450] Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., H/F or Y); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P). See, e.g., Ko et al., BioDrugs 2021, 35:147-157.

[01451] In certain embodiments, a BCMAxCD3 bispecific antigen-binding molecule or a CD20xCD3 bispecific antigen-binding molecule comprises an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (e.g., T250Q and M248L); 252Y, 254T and 256E (e.g., M252Y, S254T and T256E); 428L and 434S

(e.g., M428L and N434S); and 433K and 434F (e.g., H433K and N434F).

[01452] In some embodiments, the BCMAxCD3 bispecific antigen-binding molecules or the CD20xCD3 bispecific antigen-binding molecules of the present disclosure comprise a modified Fc domain having reduced effector function. As used herein, a "modified Fc domain having reduced effector function" means any Fc portion of an immunoglobulin that has been modified, mutated, truncated, etc., relative to a wild-type, naturally occurring Fc domain such that a molecule comprising the modified Fc exhibits a reduction in the severity or extent of at least one effect selected from the group consisting of cell killing (e.g., ADCC and/or CDC), complement activation, phagocytosis and opsonization, relative to a comparator molecule comprising the wild-type, naturally occurring version of the Fc portion. In certain embodiments, a "modified Fc domain having reduced effector function" is an Fc domain with reduced or attenuated binding to an Fc receptor (e.g., FcγR).

[01453] In certain embodiments, a modified Fc domain having reduced binding to an Fc receptor (e.g., Fcγ receptor, e.g., FcγRI, FcγRIIA, FcγRIIB, or FcγRIIIA) is a variant IgG1 Fc or a variant IgG4 Fc comprising one or more substitutions or modifications in the hinge region and/or a CH region (e.g., CH2). For example, a modified Fc domain may comprise a variant IgG1 Fc wherein at least one amino acid of an IgG1 Fc hinge region and/or CH region is replaced with the corresponding amino acid from an IgG2 Fc hinge region and/or CH region. In certain embodiments, the modified Fc domain is a variant IgG1 Fc or a variant IgG4 Fc comprising one or more substitutions or modifications in the hinge region. For example, a modified Fc domain may comprise a variant IgG1 Fc, wherein at least one amino acid of the IgG1 Fc hinge region is replaced with the corresponding amino acid from the IgG2 Fc hinge region. In one example, the variant IgG1 Fc can comprise a human IgG2 lower hinge amino acid sequence or can comprise both a human IgG2 lower hinge amino acid sequence and a human IgG4 CH2 amino acid sequence. For example, in some embodiments, the heavy chain constant region can comprise a variant IgG1 Fc in which positions 233-236 by EU numbering are occupied by PVA. See, e.g., US 10,988,537, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the heavy chain constant region can comprise a variant IgG1 Fc in which the IgG1 CH2 region is replaced with the corresponding amino acids from the IgG4 CH2 region and in which positions 233-236 by EU numbering are occupied by PVA. Alternatively, a modified Fc domain may comprise a variant IgG4 Fc wherein at least one amino acid of an IgG4 Fc hinge region and/or CH region is replaced with the corresponding amino acid from an IgG2 Fc hinge region and/or CH region. Alternatively, a modified Fc domain may comprise a variant IgG4 Fc, wherein at least one amino acid of the IgG4 Fc hinge region is replaced with the corresponding

amino acid from the IgG2 Fc hinge region. In one example, the variant IgG4 Fc can comprise a human IgG2 lower hinge amino acid sequence. For example, in some embodiments, the heavy chain constant region can comprise a variant IgG4 Fc in which positions 233-236 by EU numbering are occupied by PVA. See, e.g., US 10,988,537, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, a modified Fc domain comprises a modified hinge region in which each of positions 233-236 by EU numbering is occupied by G or is unoccupied. In some embodiments, a modified Fc domain comprises modifications in which each of positions 233-236 by EU numbering is occupied by G or is unoccupied. For example, in some embodiments, a modified Fc domain can comprise a modified hinge region in which positions 233-236 by EU numbering are occupied by GGG. See, e.g., US 11,518,807, the disclosure of which is hereby incorporated by reference in its entirety. In some embodiments, the heavy chain constant region can comprise a variant IgG1 Fc in which the IgG1 CH2 region is replaced with the corresponding amino acids from the IgG4 CH2 region and in which positions 233-236 by EU numbering are occupied by GGG. Non-limiting, exemplary modified Fc regions that can be used in the context of the present disclosure are set forth in US Patent No. 11,518,807, the disclosure of which is hereby incorporated by reference in its entirety, as well as any functionally equivalent variants of the modified Fc regions set forth therein. Other modified Fc domains and Fc modifications that can be used in the context of the present disclosure include any of the modifications as set forth in US 8,697,396, US 10,988,537, US 2014/0171623, US 2014/0134162, US 2014/0243504, and WO 2014/043361, the disclosures of each of which are incorporated by reference herein.

[01454] All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present disclosure.

Polynucleotides, Vectors, and Host Cells

[01455] In another aspect, the present disclosure provides nucleic acid molecules comprising one or more polynucleotide sequences encoding the antigen-binding molecules disclosed herein, as well as vectors (e.g., expression vectors) encoding such polynucleotide sequences and host cells into which such vectors have been introduced.

[01456] Polynucleotides, as disclosed herein, may encode all or a portion of an antigen-binding molecule, antibody, or antigen-binding fragment as disclosed throughout the present disclosure. In some cases, a single polynucleotide may encode both a HCVR and a LCVR (e.g., defined with reference to the CDRs contained within the respective amino acid sequence-defined HCVR and LCVR, defined with reference to the amino acid sequences of the CDRs of the HCVR and

LCVR, respectively, or defined with reference to the amino acid sequences of the HCVR and LCVR, respectively) of an antibody or antigen-binding fragment, or the HCVR and LCVR may be encoded by separate polynucleotides (i.e., a pair of polynucleotides). In the latter case, in which the HCVR and LCVR are encoded by separate polynucleotides, the polynucleotides may be combined in a single vector or may be contained in separate vectors (i.e., a pair of vectors). In any case, a host cell used to express the polynucleotide(s) or vector(s) may contain the full complement of component parts to generate the antibody or antigen-binding fragment thereof. For example, a host cell may comprise separate vectors, each encoding a HCVR and a LCVR, respectively, of an antibody or antigen-binding fragment thereof as discussed above or herein. Similarly, the polynucleotide or polynucleotides, and the vector or vectors, may be used to express the full-length heavy chain and full-length light chain of an antibody as discussed above or herein. For example, a host cell may comprise a single vector with polynucleotides encoding both a heavy chain and a light chain of an antibody, or the host cell may comprise separate vectors with polynucleotides encoding, respectively, a heavy chain and a light chain of an antibody as disclosed above or herein.

[01457] In some embodiments, the nucleic acid molecule comprises one or more polynucleotide sequences encoding an antigen-binding molecule disclosed in **Table 1**.

[01458] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-BCMA HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1057, 1059, and 1061, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-BCMA HCVR comprising or consisting of the sequence of SEQ ID NO: 1055. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence of SEQ ID NO: 1054, or a polynucleotide sequence having at least 70% sequence identity, e.g., at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to SEQ ID NO: 1054.

[01459] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-CD3 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1081, 1083, and 1085, respectively; or of SEQ ID NOs: 1089, 1091, and 1093, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-CD3 HCVR comprising or consisting of the sequence of SEQ ID NO: 1079 or 1087. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence of SEQ ID NO: 1078 or 1086, or a polynucleotide sequence having at least 70% sequence identity,

e.g., at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to SEQ ID NO: 1078 or 1086.

[01460] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising an LCDR1 comprising or consisting of the amino acid sequence of SEQ ID NO: 1073, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising or consisting of the sequence of SEQ ID NO: 1071. In some embodiments, the nucleic acid molecule comprises the polynucleotide sequence of SEQ ID NO: 1070, or a polynucleotide sequence having at least 70% sequence identity, e.g., at least 75%, at least 80%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, to SEQ ID NO: 1070.

[01461] In some embodiments, compositions are provided comprising one or more nucleic acid molecules as disclosed herein. For example, in some embodiments, a composition comprises a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR and/or LCVR of a first antigen-binding domain that binds BCMA, and a second nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR and/or LCVR of a second antigen-binding domain that binds CD3. In some embodiments, a composition comprises a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of a first antigen-binding domain that binds BCMA, a second nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of a first antigen-binding domain that binds BCMA, a third nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of a second antigen-binding domain that binds CD3, and a fourth nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of a second antigen-binding domain that binds CD3. In some embodiments, an anti-BCMA HCVR comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1057, 1059, and 1061, respectively. In some embodiments, an anti-BCMA LCVR comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 1073, 1075, and 1077, respectively. In some embodiments, an anti-CD3 HCVR comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1081, 1083, and 1085, respectively; or the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1089, 1091, and 1093, respectively. In some embodiments, an anti-CD3 LCVR comprises the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 1073, 1075, and 1077, respectively.

[01462] In one embodiment, the present disclosure provides a nucleic acid molecule or nucleic acid molecules that comprise a nucleotide sequence encoding the HCVR sequence of the anti-BCMA antigen-binding domain comprising SEQ ID NO: 1055, a nucleotide sequence encoding the HCVR sequence of the anti-CD3 antigen-binding domain comprising SEQ ID NO: 1079, and a nucleotide sequence encoding the LCVR sequence comprising SEQ ID NO: 1071.

[01463] In one embodiment, the present disclosure provides a nucleic acid molecule or nucleic acid molecules that comprise a nucleotide sequence encoding the HCVR sequence of the anti-BCMA antigen-binding domain comprising SEQ ID NO: 1055, a nucleotide sequence encoding the HCVR sequence of the anti-CD3 antigen-binding domain comprising SEQ ID NO: 1087, and a nucleotide sequence encoding the LCVR sequence comprising SEQ ID NO: 1071.

[01464] In another aspect, the present disclosure also provides recombinant expression vectors carrying one or more nucleic acid molecules as disclosed herein, as well as host cells into which such vectors have been introduced. In some embodiments, the host cell is a prokaryotic cell (e.g., *E. coli*). In some embodiments, the host cell is a eukaryotic cell, such as a non-human mammalian cell (e.g., a Chinese Hamster Ovary (CHO) cell). Also provided herein are methods of producing the antigen-binding molecules of the disclosure by culturing the host cells under conditions permitting production of the antigen-binding molecules, and recovering the antigen-binding molecules so produced.

[01465] In some embodiments, the nucleic acid molecule comprises one or more polynucleotide sequences encoding an antigen-binding molecule disclosed in **Table 2**.

[01466] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-CD20 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1100, 1101, and 1102, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-CD20 HCVR comprising or consisting of the sequence of SEQ ID NO: 1097.

[01467] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-CD3 HCVR comprising the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1106, 1107, and 1108, respectively. In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an anti-CD3 HCVR comprising or consisting of the sequence of SEQ ID NO: 1099.

[01468] In some embodiments, the nucleic acid molecule comprises a polynucleotide sequence that encodes an LCVR comprising the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 1103, 1104, and 1105, respectively. In some embodiments, the nucleic acid molecule comprises a

polynucleotide sequence that encodes an LCVR comprising or consisting of the sequence of SEQ ID NO: 1098.

[01469] In some embodiments, compositions are provided comprising one or more nucleic acid molecules as disclosed herein. For example, in some embodiments, a composition comprises a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR and/or LCVR of a first antigen-binding domain that binds CD20, and a second nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR and/or LCVR of a second antigen-binding domain that binds CD3. In some embodiments, a composition comprises a first nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of a first antigen-binding domain that binds CD20, a second nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of a first antigen-binding domain that binds CD20, a third nucleic acid molecule comprising a polynucleotide sequence encoding an HCVR of a second antigen-binding domain that binds CD3, and a fourth nucleic acid molecule comprising a polynucleotide sequence encoding an LCVR of a second antigen-binding domain that binds CD3. In some embodiments, an anti-CD20 HCVR comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1100, 1101, and 1102, respectively. In some embodiments, an anti-CD20 LCVR comprises LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 1103, 1104, and 1105, respectively. In some embodiments, an anti-CD3 HCVR comprises the HCDR1, HCDR2, and HCDR3 of SEQ ID NOs: 1106, 1107, and 1108, respectively. In some embodiments, an anti-CD3 LCVR comprises the LCDR1, LCDR2, and LCDR3 of SEQ ID NOs: 1103, 1104, and 1105, respectively.

[01470] In one embodiment, the present disclosure provides a nucleic acid molecule or nucleic acid molecules that comprise a nucleotide sequence encoding the HCVR sequence of the anti-CD20 antigen-binding domain comprising SEQ ID NO: 1097, a nucleotide sequence encoding the HCVR sequence of the anti-CD3 antigen-binding domain comprising SEQ ID NO: 1099, and a nucleotide sequence encoding the LCVR sequence comprising SEQ ID NO: 1098.

[01471] In another aspect, the present disclosure also provides recombinant expression vectors carrying one or more nucleic acid molecules as disclosed herein, as well as host cells into which such vectors have been introduced. In some embodiments, the host cell is a prokaryotic cell (e.g., *E. coli*). In some embodiments, the host cell is a eukaryotic cell, such as a non-human mammalian cell (e.g., a Chinese Hamster Ovary (CHO) cell). Also provided herein are methods of producing the antigen-binding molecules of the disclosure by culturing the host cells under conditions permitting production of the antigen-binding molecules, and recovering the antigen-binding molecules so produced.

Characterization of BCMAxCD3 Bispecific Antigen-Binding Molecules

[01472] The present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies) and functional fragments thereof that bind to BCMA and CD3 (e.g., human BCMA and CD3) with high affinity.

[01473] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein) that bind BCMA and CD3 (e.g., at 25°C or 37°C) with a K_D of less than about 75 nM, e.g., as measured by surface plasmon resonance or a substantially similar assay. In certain embodiments, the antigen-binding molecules of the present disclosure bind human BCMA and CD3 with a K_D of less than about 75 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 25 nM, less than about 20 nM, less than about 15 nM, less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 500 pM, less than about 400 pM, less than about 300 pM, less than about 200 pM, less than about 100 pM, less than about 90 pM, less than about 80 pM, less than about 70 pM, less than about 60 pM, less than about 50 pM, less than about 40 pM, less than about 30 pM, less than about 20 pM, less than about 10 pM, less than about 5 pM, less than about 4 pM, less than about 2 pM, less than about 1 pM, less than about 0.5 pM, less than about 0.2 pM, less than about 0.1 pM, or less than about 0.05 pM, as measured by surface plasmon resonance or a substantially similar assay.

[01474] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein) that specifically interact (e.g., bind with) cells that express BCMA and/or CD3. The extent to which an antigen-binding molecule binds cells that express BCMA and/or CD3 can be assessed by flow cytometry. For example, in some embodiments, the present disclosure provides anti-BCMAxCD3 bispecific antibodies that specifically bind cells that express BCMA and/or CD3 on the cell surface (e.g., human plasma cells and/or T cells). In some embodiments, the disclosure provides anti-BCMAxCD3 bispecific antibodies that bind BCMA and/or CD3-expressing cells or cell lines with an EC50 value of about 10 nM or less, e.g., from about 0.5 nM to about 10 nM, e.g., an EC50 value of about 1 nM, about 1.5 nM, about 2 nM, about 2.5 nM, about 3 nM, about 3.5 nM, about 4 nM, about 4.5 nM, about 5 nM, about 5.5 nM, about 6 nM, about 6.5 nM, about 7 nM, about 7.5 nM, about 8 nM, about 8.5 nM, about 9 nM, about 9.5 nM, or about 10 nM, e.g., as determined by flow cytometry or a substantially similar assay.

Characterization of CD20xCD3 Bispecific Antigen-Binding Molecules

[01475] The present disclosure includes bispecific antigen-binding molecules (e.g., bispecific

antibodies) and functional fragments thereof that bind to CD20 and CD3 (e.g., human CD20 and CD3) with high affinity.

[01476] In some embodiments, the present disclosure includes bispecific antigen-binding molecules (e.g., bispecific antibodies as disclosed herein) that specifically interact (e.g., bind with) cells that express CD20 and/or CD3. The extent to which an antigen-binding molecule binds cells that express CD20 and/or CD3 can be assessed by an *in vitro* binding assay. For example, in some embodiments, the present disclosure provides anti-CD20xCD3 bispecific antibodies that specifically bind cells that express CD20 and/or CD3 on the cell surface (e.g., human B cells and/or T cells). In certain embodiments, the anti-CD20×CD3 bispecific antibodies bind Jurkat cells and Raji cells with an EC_{50} value of less than about 60 nM, as measured by an *in vitro* binding assay. In certain embodiments, the anti-CD20×CD3 bispecific antibodies bind CD3 or CD20 on the surface of a Jurkat or Raji cell, respectively, with an EC_{50} value of less than about 1000 mM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 75 nM, less than about 70 nM, less than about 65 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 25 nM, less than about 10 nM, less than about 5 nM, less than about 2 nM, less than about 1 nM, less than about 500 pM, less than about 100 pM, less than about 10 pM, or less than about 1 pM as measured by an *in vitro* binding assay.

Epitope Mapping and Related Technologies

[01477] In some embodiments, the epitope on BCMA and/or CD20 and/or CD3 to which the antigen-binding molecules of the present disclosure bind (e.g., an epitope of BCMA or CD20 to which a first antigen-binding domain (D1) binds, or an epitope of CD3 to which a second antigen-binding domain (D2) binds) may consist of a single contiguous sequence of 3 or more (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids of a BCMA or CD20 or CD3 protein. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) of a BCMA or CD20 or CD3 protein. The antibodies of the invention may interact with amino acids contained within a single CD3 chain (e.g., CD3-epsilon, CD3-delta or CD3-gamma), or may interact with amino acids on two or more different CD3 chains. The term “epitope,” as used herein, refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A

linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[01478] Various techniques known to persons of ordinary skill in the art can be used to determine whether an antigen-binding domain of an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques that can be used to determine an epitope or binding domain of a particular antibody or antigen-binding domain include, e.g., routine crossblocking assay such as that described in Antibodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., NY), point mutagenesis (e.g., alanine scanning mutagenesis, arginine scanning mutagenesis, etc.), peptide blots analysis (Reineke, 2004, Methods Mol Biol 248:443-463), protease protection, and peptide cleavage analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer, 2000, Protein Science 9:487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water to allow hydrogen-deuterium exchange to occur at all residues except for the residues protected by the antibody (which remain deuterium-labeled). After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues which correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) Analytical Biochemistry 267(2):252-259; Engen and Smith (2001) Anal. Chem. 73:256A-265A. X-ray crystal structure analysis can also be used to identify the amino acids within a polypeptide with which an antibody interacts.

[01479] The present disclosure also includes antigen-binding molecules (e.g., antibodies or antigen-binding domains thereof) that bind to the same epitope as, or competes for binding with, a bispecific BCMAxCD3 antigen-binding molecule or a bispecific CD20xCD3 antigen-binding molecule described herein. One skilled in the art can determine whether or not a particular antigen-binding molecule (e.g., antibody) or antigen-binding domain thereof binds to the same epitope as, or competes for binding with, a reference antigen-binding molecule of the present disclosure by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope on BCMA and/or CD20 and/or CD3 as a reference bispecific antigen-binding molecule of the present disclosure, the reference bispecific molecule is first allowed to bind to a BCMA and/or CD20 and/or CD3 protein. Next, the ability of a test antibody

to bind to the BCMA and/or CD20 and/or CD3 molecule is assessed. If the test antibody is able to bind to BCMA and/or CD20 and/or CD3 following saturation binding with the reference bispecific antigen-binding molecule, it can be concluded that the test antibody binds to a different epitope of BCMA and/or CD20 and/or CD3 than the reference bispecific antigen-binding molecule. On the other hand, if the test antibody is not able to bind to the BCMA and/or CD20 and/or CD3 molecule following saturation binding with the reference bispecific antigen-binding molecule, then the test antibody may bind to the same epitope of BCMA and/or CD20 and/or CD3 as the epitope bound by the reference bispecific antigen-binding molecule of the disclosure. Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference bispecific antigen-binding molecule or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, radioimmunoassay (RIA), Biacore, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art. In accordance with certain embodiments of the present disclosure, two antigen-binding proteins bind to the same (or overlapping) epitope if, e.g., a 1-, 2-, 5-, 10-, 20- or 100-fold excess of one antigen-binding protein inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990:50:1495-1502). Alternatively, two antigen-binding proteins are deemed to bind to the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antigen-binding protein reduce or eliminate binding of the other. Two antigen-binding proteins are deemed to have "overlapping epitopes" if only a subset of the amino acid mutations that reduce or eliminate binding of one antigen-binding protein reduce or eliminate binding of the other.

[01480] To determine if an antibody or antigen-binding domain thereof competes for binding with a reference antigen-binding molecule, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antigen-binding molecule is allowed to bind to a BCMA and/or CD20 and/or CD3 protein under saturating conditions followed by assessment of binding of the test antibody to the BCMA and/or CD20 and/or CD3 molecule. In a second orientation, the test antibody is allowed to bind to a BCMA and/or CD20 and/or CD3 molecule under saturating conditions followed by assessment of binding of the reference antigen-binding molecule to the BCMA and/or CD20 and/or CD3 molecule. If, in both orientations, only the first (saturating) antigen-binding molecule is capable of binding to the BCMA and/or CD20 and/or CD3 molecule, then it is concluded that the test antibody and the

reference antigen-binding molecule compete for binding to BCMA and/or CD20 and/or CD3. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antigen-binding molecule may not necessarily bind to the same epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Preparation of Antigen-Binding Domains and Construction of Multispecific Antigen-Binding Molecules

[01481] Antigen-binding domains specific for particular antigens can be prepared by any antibody generating technology known in the art. Once obtained, two different antigen-binding domains can be appropriately arranged relative to one another to produce a bispecific antigen-binding molecule of the present disclosure using routine methods. A discussion of exemplary bispecific antibody formats that can be used to construct the bispecific antigen-binding molecules of the present disclosure is provided elsewhere herein. In certain embodiments, one or more of the individual components (e.g., heavy, and light chains) of the multispecific antigen-binding molecules are derived from chimeric, humanized or fully human antibodies. Methods for making such antibodies are well known in the art. For example, one or more of the heavy and/or light chains of the bispecific antigen-binding molecules of the present disclosure can be prepared using VELOCIMMUNE™ technology. Using VELOCIMMUNE™ technology (or any other human antibody generating technology), high affinity chimeric antibodies to a particular antigen (e.g., BCMA or CD20 or CD3) are initially isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate fully human heavy and/or light chains that can be incorporated into the bispecific antigen-binding molecules.

[01482] In some embodiments, genetically engineered animals may be used to make human bispecific antigen binding molecules. For example, a genetically modified mouse can be used which is incapable of rearranging and expressing an endogenous mouse immunoglobulin light chain variable sequence, wherein the mouse expresses only one or two human light chain variable domains encoded by human immunoglobulin sequences operably linked to the mouse kappa constant gene at the endogenous mouse kappa locus. Such genetically modified mice can be used to produce fully human bispecific antigen-binding molecules comprising two different heavy chains that associate with an identical light chain that comprises a variable domain derived from one of two different human light chain variable region gene segments. See, e.g., US 2011/0195454, the entire contents of which are incorporated herein by reference,

for a detailed discussion of such engineered mice and the use thereof to produce bispecific antigen-binding molecules. As used herein, "fully human" refers to an antigen-binding molecule, e.g., an antibody, or antigen-binding fragment or immunoglobulin domain thereof, comprising an amino acid sequence encoded by a DNA derived from a human sequence over the entire length of each polypeptide of the antigen-binding molecule, antibody, antigen-binding fragment, or immunoglobulin domain thereof. In some instances, the fully human sequence is derived from a protein endogenous to a human. In other instances, the fully human protein or protein sequence comprises a chimeric sequence wherein each component sequence is derived from human sequence. While not being bound by any one theory, chimeric proteins or chimeric sequences are generally designed to minimize the creation of immunogenic epitopes in the junctions of component sequences, e.g., compared to any wild-type human immunoglobulin regions or domains.

Bioequivalents

[01483] The present disclosure encompasses antigen-binding molecules having amino acid sequences that vary from those of the described antibodies but that retain the ability to bind BCMA and/or CD20 and/or CD3. Such variant molecules comprise one or more additions, deletions, or substitutions of amino acids when compared to the parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antigen-binding molecules. Likewise, the nucleic acid sequences encoding the antigen-binding molecules of the present disclosure encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antigen binding molecule that is essentially bioequivalent to the antigen-binding molecules disclosed herein.

[01484] The present disclosure includes antigen-binding molecules that are bioequivalent to any of the exemplary antigen-binding molecules set forth herein. Two antigen-binding proteins, e.g., bispecific antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple doses. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

[01485] In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

[01486] In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the first antigen-binding protein (e.g., reference product) and the second antigen-binding protein (e.g., biological product) without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

[01487] In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

[01488] Bioequivalence may be demonstrated by *in vivo* and *in vitro* methods. Non-limiting examples of bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

[01489] Bioequivalent variants of the exemplary bispecific antigen-binding molecules set forth herein may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other embodiments, bioequivalent antibodies may include the exemplary bispecific antigen-binding molecules set forth herein comprising amino acid changes which modify the glycosylation characteristics of the antibodies, e.g., mutations which eliminate or remove glycosylation.

B Cell Depleting Agents

[01490] As used herein, a "B cell depleting agent" refers to any molecule capable of specifically binding to a surface antigen on B cells and killing or depleting said B cell. Thus, in general, a B cell depleting agent can be any agent that binds to a B cell surface molecule. In some embodiments, the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

[01491] In various aspects, the present disclosure provides B cell depleting agents combined

with, or administered in combination with, plasma cell depleting agents (e.g., an anti-BCMAxCD3 bispecific antibody, or a functional fragment thereof) described herein to subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the B cell depleting agent may be administered to subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) not only in combination with a plasma cell depleting agent but also in combination with an immunoglobulin depleting agent (e.g., an FcFn blocker such as, e.g., efgartigimod), plasmapheresis, therapeutic plasma exchange, or immunoadsorption, and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) disclosed herein. Suitable combinations comprising a plasma cell depleting agent are described in more detail elsewhere herein.

[01492] In some embodiments, the B cell depleting agent is an agent that directly targets a B cell, e.g., an agent that binds to a B cell surface molecule. In some embodiments, the B cell depleting agent causes a reduction in the number of B cells in a subject (e.g., in a blood sample taken from the subject). In some embodiments, a B cell depleting agent may be useful for, e.g., eliminating non-plasma cell (e.g., non-long-lived plasma cell [LLPC]) sources of immunogen (e.g., anti-AAV) nAbs. In some embodiments, the B cell depleting agent may capture a wider range of AAV-specific B cells and plasma cells that may not express high levels of BCMA (e.g., committed memory B cells and early plasmablasts).

[01493] In some embodiments, the B cell depleting agent comprises an anti-CD19 antibody (e.g., MEDI-551, tefasitamab, Inebilizumab, loncastuximab), an anti-CD20 antibody (e.g., rituximab, ocrelizumab, obinutuzumab, ublituximab, or ofatumumab), an anti-CD22 antibody (e.g., epratuzumab), an anti-CD79 antibody (polatuzumab), a bispecific anti-CD20xCD3 B cell depleting antibody (e.g. odronextamab, glofitamab, mosunetuzumab, epcoritamab), a bispecific anti-CD19xCD3 antibody (blinatumomab), a bispecific anti-CD22xCD3 antibody (inotuzumab), or functional fragments thereof, or any combination thereof.

[01494] In some embodiments, the B cell depleting agent is an agent that indirectly targets a B cell, e.g., by targeting a B cell survival factor. In some embodiments, the B cell depleting agent is a BLyS/BAFF inhibitor (e.g., belimumab, lanalumab, BR3-Fc, AMG-570, or AMG-623), an APRIL inhibitor (e.g., telitacicept, atacicept), or a BLyS receptor 3/BAFF receptor inhibitor (e.g., anti-BR3), or any combination thereof.

[01495] In some embodiments, the B cell depleting agent is selected from anti-CD19 antibodies, anti-CD20 antibodies, anti-CD22 antibodies, anti-CD79 antibodies, multispecific

antibodies combining two or more of any of said antibody specificities, multispecific antibodies combining any of said antibody specificities with anti-CD3 antibodies, functional fragments of any of said antibodies, and any combinations thereof. In some embodiments, the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof. In certain embodiments, the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof. In some embodiments, a multispecific anti-CD20 antibody or functional fragment thereof of the present disclosure targets CD20 and CD19. In some embodiments the multispecific anti-CD20 antibody or functional fragment thereof is anti-CD19xCD20 bispecific antibody, or functional fragment thereof.

[01496] In some embodiments, the B cell depleting agent comprises anti-CD19 and anti-CD20 antibodies (also referred to as "anti-CD19/CD20 antibodies" herein), or functional fragments thereof, disclosed herein.

[01497] In a specific embodiment, the B cell depleting agent comprises a bispecific antibody that specifically binds CD3 and CD19. Such antibodies may be referred to herein as, e.g., "anti-CD19/anti-CD3," or "anti- CD19×CD3" or "CD19×CD3" bispecific antibodies, or other similar terminology.

[01498] In a specific embodiment, the B cell depleting agent comprises a bispecific antibody that specifically binds CD3 and CD20. Such antibodies may be referred to herein as, e.g., "anti-CD20/anti-CD3," or "anti-CD20×CD3" or "CD20×CD3" bispecific antibodies, or other similar terminology.

[01499] As used herein, the expression "bispecific antibody" in the context of CD20×CD3 bispecific antibodies refers to an immunoglobulin protein comprising at least a first antigen-binding domain and a second antigen-binding domain. In some embodiments, the first antigen-binding domain specifically binds a first antigen (e.g., CD20), and the second antigen-binding domain specifically binds a second, distinct antigen (e.g., CD3). Each antigen-binding domain of a bispecific antibody comprises a heavy chain variable domain (HCVR) and a light chain variable domain (LCVR), each comprising three CDRs. In the context of a bispecific antibody, the CDRs of the first antigen-binding domain may be designated with the prefix "A" and the CDRs of the second antigen-binding domain may be designated with the prefix "B." Thus, the CDRs of the first antigen-binding domain may be referred to herein as A-HCDR1, A-HCDR2, and A-HCDR3; and the CDRs of the second antigen-binding domain may be referred to herein as B-HCDR1, B-HCDR2, and B-HCDR3.

[01500] The first antigen-binding domain and the second antigen-binding domain are each connected to a separate multimerizing domain. As used herein, a "multimerizing domain" is any

macromolecule, protein, polypeptide, peptide, or amino acid that has the ability to associate with a second multimerizing domain of the same or similar structure or constitution. In the context of the present disclosure, the multimerizing component is an Fc portion of an immunoglobulin (comprising a C_H2-C_H3 domain), e.g., an Fc domain of an IgG selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group.

[01501] Bispecific antibodies of the present disclosure typically comprise two multimerizing domains, e.g., two Fc domains that are each individually part of a separate antibody heavy chain. The first and second multimerizing domains may be of the same IgG isotype such as, e.g., IgG1/IgG1, IgG2/IgG2, IgG4/IgG4. Alternatively, the first and second multimerizing domains may be of different IgG isotypes such as, e.g., IgG1/IgG2, IgG1/IgG4, IgG2/IgG4, etc.

[01502] Any bispecific antibody format or technology may be used to make the bispecific antigen-binding molecules of the present disclosure. For example, an antibody or fragment thereof having a first antigen binding specificity can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment having a second antigen-binding specificity to produce a bispecific antigen-binding molecule. Specific exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, e.g., scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (e.g., common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED)body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab2 bispecific formats (see, e.g., Klein et al. 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats).

[01503] In the context of bispecific antibodies of the present disclosure, Fc domains may comprise one or more amino acid changes (e.g., insertions, deletions or substitutions) as compared to the wild-type, naturally occurring version of the Fc domain. For example, the disclosure includes bispecific antigen-binding molecules comprising one or more modifications in the Fc domain that results in a modified Fc domain having a modified binding interaction (e.g., enhanced or diminished) between Fc and FcRn. In one embodiment, the bispecific antigen-binding molecule comprises a modification in a C_H2 or a C_H3 region, wherein the modification increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Non-limiting examples of such Fc modifications are disclosed in US 2015/0266966, incorporated herein in its entirety.

[01504] The present disclosure also includes bispecific antibodies comprising a first C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from

one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V821 (by IMGT; D356E, L358M, N384S, K392N, V397M, and V4221 by EU) in the case of IgG1 antibodies; N44S, K52N, and V821 (IMGT; N384S, K392N, and V4221 by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V821 (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V4221 by EU) in the case of IgG4 antibodies.

[01505] In certain embodiments, the Fc domain may be chimeric, combining Fc sequences derived from more than one immunoglobulin isotype. For example, a chimeric Fc domain can comprise part or all of a C_H2 sequence derived from a human IgG1, human IgG2 or human IgG4 C_H2 region, and part or all of a C_H3 sequence derived from a human IgG1, human IgG2 or human IgG4. A chimeric Fc domain can also contain a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" sequence, derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence, derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. A particular example of a chimeric Fc domain that can be included in any of the antigen-binding molecules set forth herein comprises, from N- to C-terminus: [IgG4 C_H1]-[IgG4 upper hinge]-[IgG2 lower hinge]-[IgG4 C_H2]-[IgG4 C_H3]. Another example of a chimeric Fc domain that can be included in any of the antigen-binding molecules set forth herein comprises, from N- to C-terminus: [IgG1 C_H1]-[IgG1 upper hinge]-[IgG2 lower hinge]-[IgG4 C_H2] [IgG1 C_H3]. These and other examples of chimeric Fc domains that can be included in any of the antigen-binding molecules of the present disclosure are described in US Patent Publication No. 2014/0243504, which is herein incorporated in its entirety. Chimeric Fc domains having these general structural arrangements, and variants thereof, can have altered Fc receptor binding, which in turn affects Fc effector function.

CD20xCD3 Antigen-Binding Molecules

[01506] The term "CD20," as used herein, refers to an antigen which is expressed on B cells and which consists of a non-glycosylated phosphoprotein expressed on the cell membranes of mature B cells. The human CD20 protein can have the amino acid sequence as in NCBI Reference Sequence NP_690605.1. As used herein, the expression "anti-CD20 antibody"

includes monovalent antibodies with a single specificity, such as RITUXAN® (rituximab), as described in U.S. Pat. No. 7,879,984. Exemplary anti-CD20 antibodies are also described in U.S. Pat. No. 7,879,984 and PCT International Application No. PCT/US2013/060511, filed on Sep. 19, 2013, each incorporated by reference herein.

[01507] In some exemplary embodiments, the CD20 targeting agent used in the disclosed methods is a multispecific (e.g., bispecific) antibody, or a functional fragment thereof, that specifically binds CD20 and CD3 (e.g., an anti-CD20×CD3 bispecific antibody). The anti-CD20xCD3 multispecific (e.g., bispecific) antibodies are useful for specific targeting and T-cell-mediated killing of cells that express CD20. The terms "antibody," "antigen-binding fragment," "human antibody," "recombinant antibody," and other related terminology are defined above. In the context of anti-CD20xCD3 antibodies and antigen-binding fragments thereof, the present disclosure includes the use of bispecific antibodies wherein one arm of an immunoglobulin is specific for CD20 or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target (e.g., CD3 on T-cells). Exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, e.g., scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (e.g., common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED) body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mabe bispecific formats (see, e.g., Klein et al. 2012, mAbs 4(6):653-663, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, e.g., wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (See, e.g., Kazane et al., J. Am. Chem. Soc., 2013, 135(1):340-46).

[01508] The anti-CD20×CD3 bispecific antibodies are capable of simultaneously binding to human CD3 and human CD20. According to certain embodiments, the anti-CD20×CD3 bispecific antibodies specifically interact with cells that express CD3 and/or CD20. The extent to which the anti-CD20×CD3 bispecific antibodies binds cells that express CD3 and/or CD20 can be assessed by fluorescence activated cell sorting (FACS). In certain embodiments, the anti-CD20×CD3 bispecific antibodies specifically bind human T-cell lines which express CD3 (e.g., Jurkat), human B-cell lines which express CD20 (e.g., Raji), and primate T-cells (e.g., cynomolgus peripheral blood mononuclear cells [PBMCs]).

[01509] In some embodiments, the anti-CD20xCD3 bispecific antigen-binding molecule comprises a first antigen-binding domain (D1) that binds an epitope of CD20 (e.g., human

CD20), and a second antigen-binding domain (D2) that binds an epitope of CD3 (e.g., human CD3).

[01510] According to certain exemplary embodiments, the bispecific anti-CD20/anti-CD3 antibody, or antigen-binding fragment thereof comprises heavy chain variable regions (A-HCVR and B-HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the bispecific anti-CD20/anti-CD3 antibodies as set forth in US Patent Publication No. 20150266966, incorporated herein by reference in its entirety. In certain exemplary embodiments, the bispecific anti-CD20/anti-CD3 antibody or antigen-binding fragment thereof that can be used in the context of the methods of the present disclosure comprises: (a) a first antigen-binding arm comprising the heavy chain complementarity determining regions (A-HCDR1, A-HCDR2 and A-HCDR3) of a heavy chain variable region (A-HCVR) comprising the amino acid sequence of SEQ ID NO: 1097 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098; and (b) a second antigen-binding arm comprising the heavy chain CDRs (B-HCDR1, B-HCDR2 and B-HCDR3) of a HCVR (B-HCVR) comprising the amino acid sequence of SEQ ID NO: 1099 and the light chain CDRs of a LCVR comprising the amino acid sequence of SEQ ID NO: 1098. According to certain embodiments, the A-HCDR1 comprises the amino acid sequence of SEQ ID NO: 1100; the A-HCDR2 comprises the amino acid sequence of SEQ ID NO: 1101; the A-HCDR3 comprises the amino acid sequence of SEQ ID NO: 1102; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 1103; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 1104; the LCDR3 comprises the amino acid sequence of SEQ ID NO: 1105; the B-HCDR1 comprises the amino acid sequence of SEQ ID NO: 1106; the B-HCDR2 comprises the amino acid sequence of SEQ ID NO: 1107; and the B-HCDR3 comprises the amino acid sequence of SEQ ID NO: 1108. In yet other embodiments, the bispecific anti-CD20/anti-CD3 antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding arm comprising a HCVR (A-HCVR) comprising SEQ ID NO: 1097 and a LCVR comprising SEQ ID NO: 1098; and (b) a second antigen-binding arm comprising a HCVR (B-HCVR) comprising SEQ ID NO: 1099 and a LCVR comprising SEQ ID NO: 1098.

[01511] Other bispecific anti-CD20/anti-CD3 antibodies that can be used in the context of the methods of the present disclosure include, e.g., any of the antibodies as set forth in US 2014/0088295, US 2015/0166661, and US 2017/0174781, the disclosure of each of which is incorporated by reference in its entirely. An exemplary bispecific anti-CD20/anti-CD3 antibody that can be used in the context of the methods of the present disclosure is the bispecific anti-

CD20/anti-CD3 antibody known as REGN1979 or bsAB1.

[01512] In some exemplary embodiments, an anti-CD20xCD3 bispecific antibody or antigen-binding fragment thereof that can be used in the context of the present disclosure comprising a HCVR, a LCVR, and/or CDRs comprising the amino acid sequences of REGN1979 as set forth in **Table 2** below.

Table 2. Amino Acid Sequences of Exemplary Anti-CD20×CD3 Bispecific Antibodies.

	Anti-CD20 First Antigen-Binding Domain				Anti-CD3 Second Antigen-Binding Domain				Common Light Chain Variable Region			
Bispecific antibody identifier	HCVR	HCDR1	HCDR2	HCDR3	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
REGN1979	1097	1100	1101	1102	1099	1106	1107	1108	1098	1103	1104	1105

SEQ ID NO: 1097 – Anti-CD20 HCVR Protein Sequence

EVQLVESGGGLVQPGRSLRLSCVASGFTFNDYAMHWVRQAPGKGLEWVSVISWNSDSIGYADSVKGRFTISRDNAKN
SLYLQMHSLRAEDTALYYCAKDNHYGSGSYYYYQYGMDVWGQGTTVTVSS

SEQ ID NO: 1098– Common LCVR Protein Sequence

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISS
LQSEDFAVYYCQHYINWPLTFGGGTKVEIKR

SEQ ID NO: 1099– Anti-CD3 HCVR Protein Sequence

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYTMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKK
SLYLQMNSLRAEDTALYYCAKDNSGYGHYYYGMDVWGQGTTVTVAS

SEQ ID NO: 1100 – Anti-CD20 HCDR1 Protein Sequence

GFTFNDYA

SEQ ID NO: 1101 – Anti-CD20 HCDR2 Protein Sequence

ISWNSDSI

SEQ ID NO: 1102 – Anti-CD20 HCDR3 Protein Sequence

AKDNHYGSGSYYYYQYGMDV

SEQ ID NO: 1103 – Common LCDR1 Protein Sequence

QSVSSN

SEQ ID NO: 1104 – Common LCDR2 Protein Sequence
GAS

SEQ ID NO: 1105 – Common LCDR3 Protein Sequence
QHYINWPLT

SEQ ID NO: 1106 – Anti-CD3 HCDR1 Protein Sequence
GFTFDDYT

SEQ ID NO: 1107 – Anti-CD3 HCDR2 Protein Sequence
ISWNSGSI

SEQ ID NO: 1108 – Anti-CD3 HCDR3 Protein Sequence
AKDNSGYGHYYYGMDV

[01513] In some embodiments, the anti-CD20xCD3 bispecific antibody or antigen-binding fragment thereof that can be used in the present disclosure comprises: (a) a first antigen binding domain that binds specifically to CD20; and (b) a second antigen-binding domain that binds specifically to CD3. In one embodiment, the anti-CD20 antigen-binding domain comprises the heavy chain complementarity determining regions (A-HCDRs) of a heavy chain variable region (A-HCVR) comprising the amino acid sequence of SEQ ID NO: 1097 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098. In one embodiment, the first antigen-binding domain comprises three HCDRs (A-HCDR1, A-HCDR2 and A-HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the A-HCDR1 comprises the amino acid sequence of SEQ ID NO: 1100; the A-HCDR2 comprises the amino acid sequence of SEQ ID NO: 1101; the A-HCDR3 comprises the amino acid sequence of SEQ ID NO: 1102; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 1103; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 1104; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 1105.

[01514] In one embodiment, the second antigen-binding domain comprises the heavy chain complementarity determining regions (B-HCDRs) of a heavy chain variable region (B-HCVR) comprising the amino acid sequence of SEQ ID NO: 1099 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid

sequence of SEQ ID NO: 1098. In one embodiment, the second antigen-binding domain comprises three HCDRs (B-HCDR1, B-HCDR2 and B-HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the B-HCDR1 comprises the amino acid sequence of SEQ ID NO: 1106; the B-HCDR2 comprises the amino acid sequence of SEQ ID NO: 1107; the B-HCDR3 comprises the amino acid sequence of SEQ ID NO: 1108; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 1103; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 1104; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 1105.

[01515] In one embodiment, the anti-CD20xCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises A-HCDR1, A-CDR2, and A-HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, and LCDR1, LCDR2, and LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105; and (b) a second antigen binding domain that comprises B-HCDR1, B-HCDR2, and B-HCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, and LCDR1, LCDR2, and LCDR3 domains, respectively, comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105. In one embodiment, the anti-CD20xCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises a A-HCVR comprising the amino acid sequence of SEQ ID NO: 1097 and a LCVR comprising the amino acid sequence of SEQ ID NO: 1098; and (b) a second antigen-binding domain that comprises a B-HCVR comprising the amino acid sequence of SEQ ID NO: 1099 and a LCVR comprising the amino acid sequence of SEQ ID NO: 1098.

[01516] Exemplary anti-CD20xCD3 bispecific antibodies include the fully human bispecific antibody known as REGN1979. *See, e.g.,* US 2014/0088295, US 2015/0166661, and US 2017/0174781, each of which is herein incorporated by reference. According to certain exemplary embodiments, the methods of the present disclosure comprise the use of REGN1979, or a bioequivalent thereof. As used herein, the term "bioequivalent" with respect to anti-CD20xCD3 antibodies refers to antibodies or CD20xCD3 binding proteins or fragments thereof that are pharmaceutical equivalents or pharmaceutical alternatives having a rate and/or extent of absorption that does not show a significant difference with that of a reference antibody (e.g., REGN1979) when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose; the term "bioequivalent" also includes antigen-binding proteins that bind to CD20/CD3 and do not have clinically meaningful differences with the reference antibody (e.g., REGN1979) with respect to safety, purity, and/or potency.

[01517] In some embodiments, the anti-CD20xCD3 bispecific antibody or antigen-binding

fragment thereof comprises: (a) a first antigen-binding domain that comprises a A-HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1097 and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1098; and (b) a second antigen-binding domain that comprises a B-HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1099 and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1098. In some embodiments, the anti-CD20xCD3 bispecific antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding domain that comprises three HCDRs (A-HCDR1, A-HCDR2 and A-HCDR3) comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and an A-HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1097, and comprises three LCDRs (LCDR1, LCDR2 and LCDR3) comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively, and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1098; and (b) a second antigen-binding domain that comprises three HCDRs (B-HCDR1, B-HCDR2 and B-HCDR3) comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and a B-HCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1099, and comprises three LCDRs (LCDR1, LCDR2 and LCDR3) comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively, and a LCVR having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to the amino acid sequence of SEQ ID NO: 1098.

[01518] The present disclosure also includes variants of the anti-CD20xCD3 antibodies described herein comprising any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein with one or more conservative amino acid substitutions. For example, the present disclosure includes use of anti-CD20xCD3 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein. In some embodiments, the disclosure includes use of an anti-CD20xCD3 antibody having HCVR, LCVR, and/or CDR amino acid sequences with 1, 2, 3, or 4 conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[01519] In some embodiments, the CDRs disclosed herein are identified according to the Kabat definition. In some embodiments, the CDRs are identified according to the Chothia definition. In some embodiments, the CDRs are identified according to the AbM definition. In some embodiments, the CDRs are identified according to the IMGT definition.

[01520] In some embodiments, the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region. In some embodiments, the human IgG heavy chain constant region is isotype IgG4 or IgG1. In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that reduces binding to an Fc receptor. In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn). In some embodiments, the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

Immunoglobulin Depleting Agents

[01521] In various aspects, the present disclosure provides immunoglobulin depleting agents combined with or administered to subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) in combination with plasma cell depleting agents (e.g., an anti-BCMAxCD3 bispecific antibody, or a functional fragment thereof) described herein. In some embodiments, the immunoglobulin depleting agent is administered to subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) not only in combination with a plasma cell depleting agent but also in combination with a B cell depleting agent, plasmapheresis, therapeutic plasma exchange, immunoadsorption, and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) disclosed herein. Suitable combinations comprising a plasma cell depleting agent are described in more detail elsewhere herein. In some embodiments, an immunoglobulin depleting agent may be useful for, e.g., accelerating IgG clearance. In some embodiments, an immunoglobulin depleting agent is capable of accelerating IgG serum clearance.

[01522] In some embodiments, an immunoglobulin depleting agent may comprise a neonatal Fc receptor (FcRn) blocker such as, but not limited to, efgartigimod alfa. The mechanistic concept of FcRn-targeting therapeutics is to accelerate IgG catabolism by blocking the FcRn-mediated intracellular IgG recycling pathway, thereby reducing overall plasma IgG levels. FcRn can participate in the maintenance of IgG levels by salvaging IgG from lysosomal degradation,

thereby prolonging the half-life of IgG. In some embodiments, FcRn blockers can compete with IgG for binding to FcRn. Due to their higher affinity for FcRn, FcRn blockers can prevent IgG from binding to FcRn and, instead, IgG is transported to the lysosome and degraded, thereby leading to decreased circulating levels of IgG.

[01523] In some embodiments, an FcRn blocker can include Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), or any combination thereof. See, e.g., Zuercher et al. (2019) Autoimmun. Rev. 18(10):102366.

[01524] In some embodiments, an immunoglobulin depleting agent may comprise an IgG degrading enzyme such as IdeS (imlifidase), IdeE (KJ103) (such as described by, e.g., Cao et al., 2025), IdeZ, or IdeXork. IdeS (imlifidase) is an endopeptidase derived from *Streptococcus pyogenes* which has specificity for human IgG, and when infused intravenously results in rapid cleavage of IgG. IdeZ (immunoglobulin-degrading enzyme from *Streptococcus equi* subspecies *zooepidemicus*) is an engineered recombinant protease overexpressed in *Escherichia coli*. IdeZ specifically cleaves IgG molecules below the hinge region to yield F(ab´)2 and Fc fragments. IdeXork (Xork) is yet another example of an IgG protease. More particular non-limiting examples of IgG degrading enzymes include Imlifidase / IdeS / Fabricator, IdeE (KJ103), IdeZ, IceMG, CYR-212, CYR-241, S-1117, HNSA-5487, and Xork. In some embodiments, an immunoglobulin depleting agent may facilitate IgG degradation via lysosomal destruction. A non-limiting example of an immunoglobulin depleting agent which may facilitate IgG degradation via lysosomal destruction is BHV-1300.

Plasmapheresis, Therapeutic Plasma Exchange, and Immunoadsorption

[01525] In various aspects, the methods disclosed herein can include plasmapheresis, therapeutic plasma exchange, or immunoadsorption in subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). These can be combined, for example, with treatment with plasma cell depleting agents (e.g., an anti-BCMAxCD3 bispecific antibody, or a functional fragment thereof) or with not only treatment with plasma cell depleting agents but also treatment with B cell depleting agents (e.g., an anti-CD20xCD3 bispecific antibody, or a functional fragment thereof), and/or immunoglobulin depleting agents described herein in subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the plasmapheresis, therapeutic plasma exchange, or immunoadsorption may be

performed in combination with treatment with a plasma cell depleting agent or in combination with treatment with a plasma cell depleting agent and a B cell depleting agent, and/or an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) disclosed herein in subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). Suitable combinations comprising a plasma cell depleting agent are described in more detail elsewhere herein. Plasmapheresis, therapeutic plasma exchange, and immunoadsorption may be useful strategies for removal of AAV antibodies from patients' blood plasma.

[01526] Plasmapheresis is a process used to selectively remove blood components used to treat a variety of conditions including those caused by the acute overproduction of antibodies (e.g., autoimmunity, transplant rejection), in which removal of pathogenic immunoglobulins results in clinical benefit. Immunoadsorption is a selective therapeutic apheresis technique by which immunoglobulins are selectively removed from patients' plasma. The immunoadsorption can be, for example, total immunoglobulin immunoadsorption. See, e.g., Boedecker-Lips et al. (2023) J. Clin. Apher. 38(5):590-601. Alternatively, the immunoadsorption can be AAV capsid specific immunoadsorption. See, e.g., Bertin et al. (2020) Sci. Rep. 10:864.

Combinations Comprising a Plasma Cell Depleting Agent

[01527] A plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) can be administered either alone, or in combination with, a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule), an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod), and/or an immunogen. In some embodiments, the administration of the plasma cell depleting agent can be further combined with plasmapheresis, therapeutic plasma exchange, and/or immunoadsorption to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). Any such plasma cell depleting agents or combinations can also be administered in combination with a CD40 inhibitor in scenarios such as those described in detail elsewhere herein. Such scenarios include, for example: (1) a plasma cell depleting agent or a combination comprising a plasma cell depleting agent as disclosed herein [e.g., in combination with a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) and/or an immunoglobulin depleting agent and/or plasmapheresis, therapeutic plasma exchange, or immunoadsorption] is used to eliminate preexisting immunity to an immunogen (e.g., AAV), while a CD40 inhibitor is used to prevent any new antibody response to the immunogen on subsequent immunogen exposure; (2) a plasma cell depleting agent or a combination comprising a plasma cell depleting agent as disclosed herein is used to

eliminate potential residual antibody responses generated following immunogen (e.g., AAV) exposure in the presence of CD40 blockade (e.g., if CD40 blockade is not completely effective); or (3) CD40 blockade is used concurrently with a plasma cell depleting agent or a combination comprising a plasma cell depleting agent as disclosed herein to block ongoing antibody responses to an immunogen (e.g., AAV) from recent exposure. As used herein, the term "in combination with" e.g., a plasma cell depleting agent (or any other compound, immunomodulator or immunogen, etc.) means that additional component(s) may be administered prior to, concurrent with, or after the administration of the plasma cell depleting agent (or any other compound, immunomodulator or immunogen, etc.). The different components of the combination can be formulated into a single composition, e.g., for simultaneous delivery, or formulated separately into two or more compositions (e.g., a kit including each component, for example, wherein the further agent is in a separate formulation).

[01528] For example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) can be administered either alone, or in combination with, a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) and/or an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod) to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent. In some embodiments, the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

[01529] In one example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) to a subject in need thereof with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01530] In another example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod) to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the immunoglobulin depleting agent comprises an FcRn blocker. In some embodiments, the immunoglobulin depleting agent comprises an IgG degrading enzyme.

[01531] In some embodiments, the combination of the plasma cell depleting agent and the

immunoglobulin depleting agent, when administered in further combination with an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) to a subject in need thereof, decreases a level of an anti-immunogen antibody titer (e.g., an anti-AAV antibody titer) in the subject (e.g., such as can be measured in a serum sample isolated from the subject). In some embodiments, the level of the anti-immunogen antibody titer is decreased by about 1-fold to about 20-fold, about 2-fold to about 15-fold, about 4-fold to about 10-fold, about 3-fold to about 18-fold, about 5-fold to about 12-fold, or about 6-fold to about 8-fold, as compared to the level of the anti-immunogen antibody titer in a subject administered the immunogen alone. In some embodiments, the anti-immunogen antibody titer is decreased by about 1-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 11-fold, about 12-fold, about 13-fold, about 14-fold, about 15-fold, about 16-fold, about 17-fold, about 18-fold, about 19-fold, or about 20-fold, or more. In some embodiments, the anti-immunogen antibody titer is decreased by about 20-fold.

[01532] In another example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) and an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod) to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the immunoglobulin depleting agent comprises an FcRn blocker. In some embodiments, the immunoglobulin depleting agent comprises an IgG degrading enzyme.

[01533] In some embodiments, the combination of the plasma cell-depleting agent, the B cell depleting agent, and the immunoglobulin-depleting agent, when administered in further combination with an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) to a subject in need thereof, decreases the level of an anti-immunogen antibody titer (e.g., an anti-AAV antibody titer) in the subject (e.g., such as can be measured in a serum sample isolated from the subject). In some embodiments, the level of the anti-immunogen antibody titer may be decreased by about 1-fold to about 20-fold, about 2-fold to about 15-fold, about 4-fold to about 10-fold, about 3-fold to about 18-fold, about 5-fold to about 12-fold, about 6-fold to about 8-fold, about 10-fold to about 30-fold, about 20-fold to about 50-fold, about 30-fold to about 70-fold, about 40-fold to about 90-fold, or about 50-fold to about 100-fold, as compared to the level of the anti-immunogen antibody titer in a subject administered the immunogen alone. In some embodiments, the anti-immunogen antibody titer is decreased by about 1-fold, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold,

about 10-fold, about 11-fold, about 12-fold, about 13-fold, about 14-fold, about 15-fold, about 16-fold, about 17-fold, about 18-fold, about 19-fold, about 20-fold, about 25-fold, about 30-fold, about 35-fold, about 40-fold, about 45-fold, about 50-fold, about 55-fold, about 60-fold, about 65-fold, about 70-fold, about 75-fold, about 80-fold, about 85-fold, about 90-fold, about 95-fold, or about 100-fold, or more. In some embodiments, the anti-immunogen antibody titer is decreased by about 100-fold.

[01534] In another example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with plasmapheresis, therapeutic plasma exchange, or immunoadsorption to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01535] In another example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with plasmapheresis, therapeutic plasma exchange, or immunoadsorption and a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01536] In another example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with plasmapheresis, therapeutic plasma exchange, or immunoadsorption and an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod) to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the immunoglobulin depleting agent comprises an FcRn blocker. In some embodiments, the immunoglobulin depleting agent comprises an IgG degrading enzyme.

[01537] In another example, a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with plasmapheresis, therapeutic plasma exchange, or immunoadsorption, a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule), and an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod) to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, the immunoglobulin depleting agent comprises an FcRn blocker. In some embodiments, the immunoglobulin depleting agent comprises an IgG degrading enzyme.

[01538] In some embodiments, the B cell depleting agent to be used in combination with the plasma cell depleting agent in subjects with preexisting immunity against an immunogen (i.e.,

an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprises two or more B cell depleting agents (e.g., an anti-CD19 antigen-binding molecule and an anti-CD20 antigen-binding molecule). In some embodiments, the immunoglobulin depleting agent to be used in combination with the plasma cell depleting agent in subjects with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) comprises two or more immunoglobulin depleting agents (e.g., an FcRn blocker and an IgG degrading enzyme).

[01539] In embodiments in which a plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with, a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) and/or an immunoglobulin depleting agent (e.g., an FcRn blocker, such as Efgartigimod) and/or plasmapheresis, therapeutic plasma exchange, or immunoadsorption to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV), one or more or all treatments can occur together or one or more or all treatments can occur sequentially. For example, in some embodiments in which the plasma cell depleting agent (e.g., a BCMAxCD3 antigen-binding molecule) is administered in combination with an IgG degrading enzyme to a subject in need thereof with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV), the plasma cell depleting agent can be administered to the subject first, followed by the IgG degrading enzyme. In another example, in embodiments where an immunoglobulin depleting agent (e.g., FcRn blocker) is administered together with plasmapheresis, therapeutic plasma exchange, or immunoadsorption, the plasmapheresis, therapeutic plasma exchange, or immunoadsorption can be first followed by administration of the immunoglobulin depleting agent (e.g., FcRn blocker). Likewise, in embodiments in which a plasma cell depleting agent is administered in combination with a CD40 inhibitor, the treatments can occur together or one or more or all treatments can occur sequentially.

Non-limiting Examples of Methods Comprising Exemplary Immunomodulatory Agents

[01540] The methods using CD40 inhibitors can also use plasma cell depleting agents or combinations comprising plasma cell depleting agents when a subject has preexisting immunity against an immunogen to be administered (e.g., preexisting AAV immunity). Examples of such methods include the following: (1) a plasma cell depleting agent or a combination comprising a plasma cell depleting agent as disclosed herein [e.g., in combination with a B cell depleting agent (e.g., a CD20xCD3 antigen-binding molecule) and/or an immunoglobulin depleting agent

and/or plasmapheresis, therapeutic plasma exchange, or immunoadsorption] is used to eliminate preexisting immunity to an immunogen (e.g., AAV), while a CD40 inhibitor is used to prevent any new antibody response to the immunogen on subsequent immunogen exposure; (2) a plasma cell depleting agent or a combination comprising a plasma cell depleting agent as disclosed herein is used to eliminate potential residual antibody responses generated following immunogen (e.g., AAV) exposure in the presence of CD40 blockade (e.g., if CD40 blockade is not completely effective); or (3) CD40 blockade is used concurrently with a plasma cell depleting agent or a combination comprising a plasma cell depleting agent as disclosed herein to block ongoing antibody responses to an immunogen (e.g., AAV) from recent exposure. The present disclosure provides, for example, a distinct B cell immunosuppression approach that enables AAV vector re-transduction in subjects with preexisting AAV immunity at levels equal to seronegative subjects, by depleting pre-existing nAbs (e.g., via combined plasma cell and immunoglobulin depletion). Long-lived plasma cells (LLPC) mediate constitutive antibody production to most antigens and are a likely reservoir of persistent anti-AAV antibody immunity. It was discovered that pre-existing anti-AAV nAbs in subjects with preexisting AAV immunity could be directly eliminated *in vivo* by LLPC depletion with linvoseltamab, a fully-human T cell-bridging bispecific antibody targeting B cell maturation antigen and CD3 (anti-BCMAxCD3 bispecific antibody), either alone or in combination with B cell depletion (to eliminate non-LLPC sources of anti-AAV nAbs) and/or FcRn blockade (to accelerate serum IgG clearance). Such methods can use plasma cell depleting agents or combinations comprising plasma cell depleting agents to mitigate immune response in subjects with preexisting immunity and facilitate redosing of nucleic acid constructs encoding a polypeptide of interest. Optionally, the plasma cell depleting agents (e.g., BCMAxCD3 antigen-binding molecules) are used in combination with other immunosuppression methodologies, such as immunoglobulin depleting agents (e.g., FcRn blockers or IgG degrading enzymes), B cell depleting agents, plasmapheresis, therapeutic plasma exchange, immunoadsorption, broad spectrum immunosuppression, or combinations thereof. In one example, plasma cell depleting agents (e.g., BCMAxCD3 bispecific antigen-binding molecules) are used in combination with immunoglobulin depleting agents (e.g., IgG half-life reducers, such as FcRn blockers). In another example, plasma cell depleting agents (e.g., BCMAxCD3 bispecific antigen-binding molecules) are used in combination with B cell depleting agents (e.g., CD20xCD3 antigen-binding molecules). In another example, BCMAxCD3 bispecific antigen-binding molecules are used in combination with immunoglobulin depleting agents (e.g., FcRn blockers) and B cell depleting agents (e.g., CD20xCD3 antigen-binding molecules). This allows re-dosing of any

AAV gene therapy product in subjects with preexisting AAV immunity.

[01541] In some methods, optionally, the methods can further comprise administering a plasma cell depleting agent or combination comprising a plasma cell depleting agent when the subject has preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). The plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered prior to, simultaneously with, or after the immunogen. In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered prior to the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered prior to and after the immunogen. Likewise, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered prior to, simultaneously with, or after the CD40 inhibitor. In some methods, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered prior to the CD40 inhibitor. In some methods, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered simultaneously with the CD40 inhibitor. In some methods, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered after the CD40 inhibitor.

[01542] In some methods, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered in the one or more subsequent administration steps if there is no plasma cell depleting agent or combination comprising the plasma cell depleting agent in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some methods, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered in the one or more subsequent administration steps if preexisting expression and/or activity levels of the plasma cell depleting agent or combination comprising the plasma cell depleting agent are below a desired threshold level (i.e., the level necessary to achieve the desired effect) in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some methods, the method comprises measuring expression and/or activity levels of the plasma cell depleting agent or combination comprising the plasma cell depleting agent prior to the one or more subsequent administration steps in a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01543] In some methods, a therapeutically effective amount of the immunogen (e.g., an

immunogenic delivery vehicle such as, e.g., AAV) and the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to the subject when the subject has preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some methods, a therapeutically effective amount of the combination of the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) and the plasma cell depleting agent and the CD40 inhibitor or combination comprising the plasma cell depleting agent and the CD40 inhibitor is administered to the subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV).

[01544] In any of the methods disclosed herein, plasma cell depleting agents (e.g., anti-BCMAxCD3) or combinations comprising plasma cell depleting agents (e.g., combinations also comprising B cell depleting agents and/or immunoglobulin depleting agents as disclosed elsewhere herein) can be used in combination with CD40 inhibitors in different manners.

[01545] In a first example, a plasma cell depleting agent or combination comprising the plasma cell depleting agent can be used to eliminate preexisting immunity against an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), while a CD40 inhibitor can be used to prevent any new antibody response to the immunogen on subsequent immunogen exposure. For example, in a subject with preexisting antibody responses to an immunogen, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject reduce an anti-immunogen antibody response. Once anti-immunogen antibodies reach sub-neutralizing levels, a CD40 inhibitor can be administered to the subject, and the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) can be dosed thereafter, and a new antibody response against the immunogen is thereby prevented. The plasma cell depleting agent or combination comprising the plasma cell depleting agent returns the subject with preexisting immunity to an effectively immunologically naïve status, while the CD40 inhibitor preserves naïve status upon immunogen exposure, therefore allowing for immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) re-dosing in the future. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent are both administered prior to the immunogen. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent are both administered prior to the immunogen. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent are both administered prior to the immunogen. In some embodiments, the plasma cell depleting agent or combination comprising

the plasma cell depleting agent is administered prior to the CD40 inhibitor. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered simultaneously with the CD40 inhibitor.

[01546] In a second example, a CD40 inhibitor can be administered together with a plasma cell depleting agent or combination comprising the plasma cell depleting agent to block ongoing antibody responses to an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) from recent exposure. For example, in a subject with preexisting antibody responses to an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV), the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered with the CD40 inhibitor in a single or repeated dose regimen. Whereas the plasma cell depleting agent or combination comprising the plasma cell depleting agent depletes antibody-secreting cell populations, the CD40 inhibitor prevents new B cell activation and terminates ongoing B cell responses that would not otherwise be impacted by the plasma cell depleting agent treatment alone. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent are both administered prior to the immunogen. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent are both administered prior to the immunogen. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered prior to the CD40 inhibitor. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered simultaneously with the CD40 inhibitor.

[01547] In a third example, a plasma cell depleting agent or combination comprising the plasma cell depleting agent can be used to eliminate potential residual antibody responses generated following immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) exposure in the presence of CD40 blockade, thereby rescuing the ability to re-dose the immunogen. For example, a CD40 inhibitor can be administered to a subject (e.g., naïve subject without preexisting immunity to an immunogen) prior to treatment with an immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV). In some embodiments, after immunogen exposure, it is possible that reduced but measurable antibody titers are generated to the immunogen (e.g., to the AAV capsid). Treatment with the plasma depleting agent or combination comprising the plasma cell depleting agent can then be initiated to bring residual antibody titers to sub-neutralizing levels. A second immunogen (either the same or different, such as a second AAV therapeutic that is either the same or different (e.g., a second rAAV8 nucleic acid construct that is different from a first rAAV8 nucleic acid construct)) can then be

administered. In such scenarios where CD40 blockade attenuates but does not fully eliminate antibody titers to the immunogen, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be used to reduce titers to levels that enable immunogen re-dosing. In some embodiments, the CD40 inhibitor is administered prior to the immunogen (e.g., a first dose of the immunogen). In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered after the first dose of the immunogen and prior to a second dose of the immunogen. In some embodiments, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered after the first dose of the immunogen, e.g., an immunogenic delivery vehicle such as, e.g., AAV (e.g., a first rAAV8 nucleic acid construct) and prior to administration of a second immunogen, e.g., an immunogenic delivery vehicle such as, e.g., AAV (e.g., a second rAAV8 nucleic acid construct that is different from the first).

[01548] In any of the above methods, a plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with the immunogen or not simultaneously. For example, in a method comprising administering a composition or combination comprising a plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) and further comprising administering an immunogen, they can be administered separately (e.g., the plasma cell depleting agent or combination comprising the plasma cell depleting agent separately from the immunogen). For example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to the immunogen, subsequent to the immunogen, prior to and subsequent to the immunogen, or at the same time as immunogen. Any suitable methods of administering plasma cell depleting agents or combinations comprising a plasma cell depleting agent and immunogens to cells or subjects can be used, and examples of such methods are described in more detail elsewhere herein.

[01549] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 hour to about 48 hours, about 1 hour to about 24

hours, about 1 hour to about 12 hours, about 1 hour to about 6 hours, about 1 hour to about 2 hours, about 2 hours to about 48 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 2 hours to about 6 hours, about 3 hours to about 48 hours, about 6 hours to about 48 hours, about 12 hours to about 48 hours, or about 24 hours to about 48 hours prior to and/or subsequent to administration of the immunogen.

[01550] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to administering the immunogen.

[01551] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle

such as, e.g., AAV) within about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, or about 6 days to about 7 days prior to administering the immunogen.

[01552] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to and subsequent to administering immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to and subsequent to administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24

hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and subsequent to administering the immunogen.

[01553] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days after administering the immunogen.

[01554] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 1 month, within about 2 months, within about 3 months, within about 4 months, within about 5 months, within about 6 months, or within about 12 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject

with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 6 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 6 months, about 2 to about 6 months, about 3 to about 6 months, about 4 to about 6 months, about 5 to about 6 months, about 1 to about 5 months, about 1 to about 4 months, about 1 to about 3 months, or about 1 to about 2 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) more than 6 months after administering the immunogen. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 12 months or about 6 months to about 12 months after administering immunogen. In some methods, the method can comprise determining whether the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is present in the subject (e.g., from a previous administration). The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the immunogen (e.g., an immunogenic delivery vehicle such as, e.g., AAV) is still present in the subject. For example, if the immunogen is a delivery vehicle, e.g., a viral vector (e.g., a recombinant AAV vector), the method can comprise determining whether the viral vector is present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen ((e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the viral vector is still present (i.e.,

detectable) in the subject. For example, if the immunogen is a delivery vehicle, e.g., a viral vector (e.g., a recombinant AAV vector), the method can comprise determining whether viral capsid protein (e.g., AAV capsid protein) is present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the capsid protein is still present (i.e., detectable) in the subject. For example, if the immunogen is a lipid nanoparticle, the method can comprise determining whether the lipid nanoparticle components (e.g., PEG) are present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the lipid nanoparticle components are still present (i.e., detectable) in the subject. For example, if the immunogen is a lipid nanoparticle, the method can comprise determining whether certain lipid nanoparticle components are present in the subject. The method can then comprise administering the plasma cell depleting agent or combination comprising the plasma cell depleting agent to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) if the components are still present (i.e., detectable) in the subject.

[01555] In methods in which a composition or combination comprising a plasma cell depleting agent or combination comprising the plasma cell depleting agent in combination with a CD40 inhibitor is administered, the plasma cell depleting agent or combination comprising the plasma cell depleting agent and the CD40 inhibitor can be administered simultaneously to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV). Alternatively, the plasma cell depleting agent or combination comprising the plasma cell depleting agent and the CD40 inhibitor can be administered sequentially in any order. For example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to and/or after the CD40 inhibitor. In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) prior to and after the CD40 inhibitor. In

another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with and after the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) simultaneously with and before the CD40 inhibitor.

[01556] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent can be administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 hour to about 48 hours, about 1 hour to about 24 hours, about 1 hour to about 12 hours, about 1 hour to about 6 hours, about 1 hour to about 2 hours, about 2 hours to about 48 hours, about 2 hours to about 24 hours, about 2 hours to about 12 hours, about 2 hours to about 6 hours, about 3 hours to about 48 hours, about 6 hours to about 48 hours, about 12 hours to about 48 hours, or about 24 hours to about 48 hours prior to and/or subsequent to administration of the CD40 inhibitor.

[01557] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours,

about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to administering the CD40 inhibitor.

[01558] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered within about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week prior to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, or about 6 days to about 7 days prior to administering the CD40 inhibitor.

[01559] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or

about 1 week prior to and subsequent to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week prior to and subsequent to administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours, about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days prior to and subsequent to administering the CD40 inhibitor.

[01560] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours, about 8 hours, about 12 hours, about 18 hours, about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, or about 1 week after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) at least about 4 hours, at least about 8 hours, at least about 12 hours, at least about 18 hours, at least about 1 day, at least about 2 days, at least about 3 days, at least about 4 days, at least about 5 days, at least about 6 days, or at least about 1 week after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 4 hours to about 24 hours, about 4 hours to about 12 hours, about 4 hours to about 8 hours, about 8 hours to about 24 hours, about 12 hours to about 24 hours,

about 1 day to about 7 days, about 1 day to about 6 days, about 1 day to about 5 days, about 1 day to about 4 days, about 1 day to about 3 days, about 1 day to about 2 days, about 2 days to about 7 days, about 3 days to about 7 days, about 4 days to about 7 days, about 5 days to about 7 days, about 6 days to about 7 days, or about 1 day to about 3 days after administering the CD40 inhibitor.

[01561] In one example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 1 month, within about 2 months, within about 3 months, within about 4 months, within about 5 months, within about 6 months, or within about 12 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) within about 6 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 month, about 2 months, about 3 months, about 4 months, about 5 months, or about 6 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 6 months, about 2 to about 6 months, about 3 to about 6 months, about 4 to about 6 months, about 5 to about 6 months, about 1 to about 5 months, about 1 to about 4 months, about 1 to about 3 months, or about 1 to about 2 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) more than 6 months after administering the CD40 inhibitor. In another example, the plasma cell depleting agent or combination comprising the plasma cell depleting agent is administered to a subject with preexisting immunity against an immunogen (i.e., an immunogen to be administered to the subject, e.g., an immunogenic delivery vehicle such as, e.g., AAV) about 1 to about 12 months or about 6 months to about 12 months after administering the CD40

inhibitor.

EXAMPLES

[01562] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the disclosure, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Construction of anti-CD40xCD40 Bispecific Antibodies

Generation of Parental anti-CD40 Antibodies

[01563] Antibodies against CD40 were obtained by immunizing a VELOCIMMUNE® mouse (i.e., an engineered mouse comprising DNA encoding human Immunoglobulin heavy and kappa chain variable regions) with a human CD40 antigen (human CD40 extracellular domain with C-terminal MMH tag; SEQ ID NO: 53).

[01564] Following immunization, antibodies were isolated directly from antigen-positive mouse B cells, e.g., as described in U.S. Pat. No. 7,582,298, incorporated by reference herein. Using this method, fully human anti-CD40 antibodies (i.e., antibodies possessing human variable domains and human constant domains) were obtained. Antibodies generated using this method were characterized and selected for desirable characteristics, including affinity, selectivity, etc.

[01565] Anti-CD40 antibodies generated using this method include antibodies designated 30027P2, 21519P2, and 21520P2. Certain biological properties of the exemplary CD40 antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Table 3: Amino Acid Sequence Identifiers for Parental Anti-CD40 Monoclonal Antibodies

	SEQ ID NOs:									
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**HC**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**	**LC**
30027P2	2	4	6	8	18	10	12	14	16	20
21519P2	22	24	26	28	30	10	12	14	16	20
21520P2	32	34	36	38	40	10	12	14	16	20

	SEQ ID NOs:									
Antibody Designation	**HCVR**	**HCDR1**	**HCDR2**	**HCDR3**	**HC**	**LCVR**	**LCDR1**	**LCDR2**	**LCDR3**	**LC**
Iscalimab [CFZ533]	57	58	59	60	65	61	62	63	64	66
Ravagalimab [ABBV-323 ;Ab102]	67	68	69	70	75	71	72	73	74	76
BI-655064	77	78	79	80	84	81	82	83	74	85
Bleselumab	86	87	88	89	94	90	91	92	93	95
ch5D12	96	97	98	99	-	100	101	102	103	-
Lucatumumab [HCD122 or CHIR-12.12]	57	58	59	60	104	61	62	63	64	66
CHIR-5.9	105	-	-	-	107	106	-	-	-	108
Abiprubart [KPL-404]	109	110	111	112	117	113	114	115	116	118
PG102/FFP104	119	97	120	99	123/ 124	121	122	102	103	125
BIIB063	126	127	128	129	134	130	131	132	133	135
V19	136	137	138	139	-	-	-	-	-	-
V15	140	141	142	143	-	-	-	-	-	-
h2C10_H3	109	110	111	112	-	113	114	115	116	-
h2C10_H1	144	110	111	112	-	145	114	115	116	-
h2C10_H2	146	110	111	112	-	145	114	115	116	-
2C10 HP-KP	109	110	111	112	-	113	114	115	116	-
2C10 HB1-KB1	147	110	111	112	-	148	114	115	116	-
2C10 HB2-KB2	149	110	111	112	-	150	114	115	116	-
Ab101	67	68	69	70	151	71	72	73	74	76
Antibody A	152	153	79	80	155	154	82	83	74	156
Antibody A	152	153	79	80	157	154	82	83	74	156
Antibody A	152	153	79	80	158	154	82	83	74	156
Antibody A	152	153	79	80	159	154	82	83	74	156
Antibody B	77	153	79	80	160	81	82	83	74	85
Antibody B	77	153	79	80	161	81	82	83	74	85
Antibody B	77	153	79	80	162	81	82	83	74	85
Antibody B	77	153	79	80	84	81	82	83	74	85
Antibody C	163	164	165	166	171	167	168	169	170	172
Antibody C	163	164	165	166	173	167	168	169	170	172
Antibody C	163	164	165	166	174	167	168	169	170	172
Antibody C	163	164	165	166	175	167	168	169	170	172
G28.5	176	-	-	-	-	177	-	-	-	-
Y12XX-hz28 [Vh-hzl4;Vk-hz2]	178	179	180	181	186	182	183	184	185	187

	SEQ ID NOs:									
Antibody Designation	HCVR	HCDR1	HCDR2	HCDR3	HC	LCVR	LCDR1	LCDR2	LCDR3	LC
Y12XX-hz40 [Vh-hzl2;Vk-hz3]	188	179	189	181	191	190	183	184	185	192
Y12XX-hz42 [Vh-hzl4;Vk-hz3]	178	179	180	181	186	190	183	184	185	192

Table 4: Nucleic Acid Sequence Identifiers for Parental Anti-CD40 Monoclonal Antibodies

		SEQ ID NOs:								
Antibody Designation	HCVR	HCDR1	HCDR2	HCDR3	HC	LCVR	LCDR1	LCDR2	LCDR3	LC
30027P2	1	3	5	7	17	9	11	13	15	19
21519P2	21	23	25	27	29	9	11	13	15	19
21520P2	31	33	35	37	39	9	11	13	15	19

Generation of Anti-CD40xCD40 Bispecific Antibodies

[01566] Bispecific antibodies comprising a first CD40 binding arm ("first antigen-binding domain") and a second CD40 binding arm ("second antigen-binding domain") were constructed using standard methodologies, wherein the two CD40 binding arms comprise distinct HCVRs paired with a common light chain. Two different heavy chain constant regions, e.g., as described in US Patent No. 11,518,807, were used for each CD40 binding arm. Exemplary anti-CD40xCD40 bispecific antibodies were generated in accordance with the present Example and

[01567] As shown in **Table 5**, for REGN16334 and REGN16431, the first CD40-binding arm ("D1") comprises the HCVR sequences of parental antibody 21519P2 and the second CD40-binding arm ("D2") comprises the HCVR sequences of parental antibody 21520P2; REGN16334 and REGN16431 have different constant region modifications for reducing Fc receptor binding and effector function.

[01568] For REGN16335 and REGN16432, the first CD40-binding arm ("D1") comprises the HCVR sequences of parental antibody 30027P2 and the second CD40-binding arm ("D2") comprises the HCVR sequences of parental antibody 21520P2; REGN16335 and REGN16432 have different constant region modifications for reducing Fc receptor binding and effector function.

[01569] For REGN20484, the first CD40-binding arm ("D1") comprises the HCVR sequences of parental antibody 21520P2 and the second CD40-binding arm ("D2") comprises the HCVR sequences of parental antibody 30027P2.

[01570] REGN16334, REGN16335, REGN16431, REGN16432, and REGN20484 all comprise a common light chain sequence.

Table 5: Amino Acid Sequence Identifiers for Anti-CD40xCD40 Bispecific Antibodies

Bispecific Antibody Identifier		Anti-CD40 First Antigen-Binding Domain (D1)							Anti-CD40 Second Antigen-Binding Domain (D2)							Common Light Chain Variable Region				
	D1 parental arm	D1-HCVR	D1-HCDR1	D1-HCDR2	D1-HCDR3	D1 heavy chain	D2 parental arm	D2-HCVR	D2-HCDR1	D2-HCDR2	D2-HCDR3	D2 heavy chain	LCVR	LCDR1	LCDR2	LCDR3	Light chain
REGN16334	21519P2	22	24	26	28	42	21520P2	32	34	36	38	44	10	12	14	16	20
REGN16335	30027P2	2	4	6	8	46	21520P2	32	34	36	38	44	10	12	14	16	20
REGN16431	21519P2	22	24	26	28	48	21520P2	32	34	36	38	50	10	12	14	16	20
REGN16432	30027P2	2	4	6	8	52	21520P2	32	34	36	38	50	10	12	14	16	20
REGN20484	21520P2	32	34	36	38	205	30027P2	2	4	6	8	207	10	12	14	16	20

Table 6: Nucleic Acid Sequence Identifiers for Anti-CD40xCD40 Bispecific Antibodies

Bispecific Antibody Identifier	Anti-CD40 First Antigen-Binding Domain (D1)					Anti-CD40 Second Antigen-Binding Domain (D2)					Common Light Chain Variable Region			
	D1-HCVR	D1-HCDR1	D1-HCDR2	D1-HCDR3	D1 heavy chain	D2-HCVR	D2-HCDR1	D2-HCDR2	D2-HCDR3	D2 heavy chain	LCVR	LCDR1	LCDR2	LCDR3	Light chain
REGN16334	21	23	25	27	41	31	33	35	37	43	9	11	13	15	19
REGN16335	1	3	5	7	45	31	33	35	37	43	9	11	13	15	19
REGN16431	21	23	25	27	47	31	33	35	37	49	9	11	13	15	19
REGN16432	1	3	5	7	51	31	33	35	37	49	9	11	13	15	19
REGN20484	31	33	35	37	204	1	3	5	7	206	9	11	13	15	19

Example 2: Biacore Binding Kinetics of CD40 Bivalent Parental and Anti-CD40xCD40 Bispecific Antibodies

[01571] The equilibrium dissociation constants (K_D) for anti-CD40 bivalent and bispecific monoclonal antibodies (mAbs) were determined using a real-time surface plasmon resonance (SPR)-based Biacore 4000 biosensor. All binding studies were performed in 10 mM HEPES, 150 mM NaCl, 3 mM EDTA, and 0.05% v/v surfactant Tween-20, pH 7.4 (HBS-ET) running buffer at 25°C and 37°C. The Biacore CM5 sensor surface was first derivatized by amine coupling with a monoclonal mouse anti-human Fc antibody (REGN2567) to capture anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies. Different concentrations of CD40 reagents, human CD40 extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (SEQ ID NO: 1114) ("hCD40-MMH"; REGN3094; SEQ ID NO: 53), monkey CD40 extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (SEQ ID NO: 1114) ("mfCD40-MMH"; REGN3097; SEQ ID NO: 54), and mouse CD40 extracellular domain expressed with a C-terminal myc-myc-hexahistidine tag (SEQ ID NO: 1114) ("mCD40-MMH"; REGN3098; SEQ ID NO: 55), at concentrations ranging from 3.7 nM to 100 nM or 3.3 nM to 90 nM in a series of 3-fold dilutions prepared in HBS-ET running buffer were injected at a flow rate of 30 µL/min for 4 minutes or 50 µL/min for 5 minutes. The dissociation of different CD40 reagents bound to anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies was monitored for 10 minutes in HBS-ET running buffer. At the end of each cycle, the anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies capture surface was regenerated using a 12 sec injection of 20mM H_3PO_4.

[01572] The association rate (ka) and dissociation rate (kd) were determined by fitting the real-time binding sensorgrams to a 1:1 binding model with mass transport limitation using Scrubber 2.0c curve-fitting software. Binding dissociation equilibrium constant (K_D) and dissociative half-life ($t_{½}$) were calculated from the kinetic rates as: K_D (M) = k_d / k_a , and $t_{½}$ (min) = [ln(2)/(60*k_d)].

[01573] Binding kinetics parameters for different CD40 reagents to anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 25ºC and 37°C are shown in **Tables 7-12**.

[01574] As shown in **Table 7**, at 25°C, anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies bound to hCD40-MMH with K_D values ranging from 101 pM to 25.1 nM. At 25°C, anti-CD40 bivalent parental antibodies bound to mfCD40-MMH with K_D values ranging from 901 pM to 205 nM (**Table 8**). Anti-CD40 bivalent parental antibodies did not bind to mCD40-MMH at 25°C (**Table 9**).

[01575] As shown in **Table 10**, at 37°C, anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies bound to hCD40-MMH with K_D values ranging from 101 pM to 69.9 nM. At 37°C, anti-CD40 bivalent parental antibodies bound to mfCD40-MMH with K_D value 3.16 nM (**Table 11**). Anti-CD40 bivalent parental antibodies did not bind to mCD40-MMH at 37°C (**Table 12**).

Table 7: Kinetic binding parameters for the interaction of hCD40-MMH with anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 25°C

Antibody	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
21519P2 (parental)	428 ± 0.7	99.0	3.85E+05	3.39E-03	8.82E-09	3.4
21520P2 (parental)	416 ± 1	76.6	8.85E+05	2.23E-02	2.51E-08	0.5
30027P2 (parental)	233.0 ± 0.5	62.0	5.46E+05	9.98E-04	1.83E-09	11.6
REGN16431 (bispecific)	348.6 ± 23.1	61.2	1.47E+06	1.49E-04	1.01E-10	77.5
REGN16432 (bispecific)	372.4 ± 19.1	56.6	7.69E+05	1.25E-04	1.63E-10	92.3

Table 8: Kinetic binding parameters for the interaction of mfCD40-MMH with anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 25°C

Antibody	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
21519P2 (parental)	428 ± 0.4	10.3	8.86E+05	1.81E-01	2.05E-07	0.1
21520P2 (parental)	417 ± 0.4	10.1	3.00E+06	2.03E-01	6.77E-08	0.1
30027P2 (parental)	232.8 ± 0.5	63.1	1.14E+06	1.02E-03	9.01E-10	11.3
REGN16431 (bispecific)	NT	NT	NT	NT	NT	NT
REGN16432 (bispecific)	NT	NT	NT	NT	NT	NT

NT = not tested

Table 9: Kinetic binding parameters for the interaction of mCD40-MMH with anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 25°C

Antibody	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
21519P2 (parental)	426 ± 0	0.4	NB	NB	NB	NB
21520P2 (parental)	417 ± 0.6	-0.5	NB	NB	NB	NB
30027P2 (parental)	231.5 ± 0.4	0.2	NB	NB	NB	NB
REGN16431 (bispecific)	NT	NT	NT	NT	NT	NT
REGN16432 (bispecific)	NT	NT	NT	NT	NT	NT

NB = no binding was observed under the experimental conditions; NT = not tested

Table 10: Kinetic binding parameters for the interaction of hCD40-MMH with anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 37°C

Antibody	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
21519P2 (parental)	584 ± 1.7	104.6	6.35E+05	1.23E-02	1.94E-08	0.9
21520P2 (parental)	553 ± 1.1	67.2	1.15E+06	8.03E-02	6.99E-08	0.1
30027P2 (parental)	265.8 ± 0.6	66.5	6.20E+05	3.72E-03	6.00E-09	3.1
REGN16431 (bispecific)	348.6 ± 23.1	61.2	1.47E+06	1.49E-04	1.01E-10	77.5
REGN16432 (bispecific)	372.4 ± 19.1	56.6	7.69E+05	1.25E-04	1.63E-10	92.3

Table 11: Kinetic binding parameters for the interaction of mfCD40-MMH with anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 37°C

Antibody	mAb Capture Level (RU)	100 nM Ag Bound (RU)	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
21519P2 (parental)	583 ± 0.7	8.4	IC	IC	IC	IC
21520P2 (parental)	551 ± 0.5	7.7	IC	IC	IC	IC
30027P2	263.3 ± 1.1	68.5	1.05E+06	3.33E-03	3.16E-09	3.5

(parental)						
REGN16431 (bispecific)	NT	NT	NT	NT	NT	NT
REGN16432 (bispecific)	NT	NT	NT	NT	NT	NT

IC = inconclusive; NT = not tested

Table 12: Kinetic binding parameters for the interaction of mCD40-MMH with anti-CD40 bivalent parental and anti-CD40xCD40 bispecific antibodies at 37°C

Antibody	**mAb Capture Level (RU)**	**100 nM Ag Bound (RU)**	**k_a (1/Ms)**	**k_d (1/s)**	**K_D (M)**	**t½ (min)**
21519P2 (parental)	580 ± 0.1	1.6	NB	NB	NB	NB
21520P2 (parental)	548 ± 0.4	0.2	NB	NB	NB	NB
30027P2 (parental)	260.4 ± 1.1	0.2	NB	NB	NB	NB
REGN16431 (bispecific)	NT	NT	NT	NT	NT	NT
REGN16432 (bispecific)	NT	NT	NT	NT	NT	NT

NB = no binding was observed under the experimental conditions; NT = not tested

Example 3: Cross-Competition Between Different Anti-CD40 Monoclonal Antibodies

[01576] Binding competition between different anti-CD40 monoclonal antibodies (mAbs) was determined using a real time, label-free bio-layer interferometry (BLI) assay on the Octet HTX biosensor platform (Pall ForteBio Corp.). In addition to parental antibodies 21519P2, 21520P2, and 30027P2, a comparator anti-CD40 antibody (REGN11209) was also tested; this comparator has the heavy chain and light chain sequences of iscalimab (see, US 8,828,396). The entire experiment was performed at 25°C in 10 mM HEPES buffer containing 150 mM NaCl, 3 mM EDTA, 1 mg/mL BSA, 0.02% NaN_3, and 0.05% v/v Surfactant Tween-20 at pH 7.4 (HBS-EP) with the plate shaking at a speed of 1000rpm.

[01577] To assess the ability of one antibody to compete with another antibody for binding to CD40, around 0.47 nm – 0.54 nm of recombinant human CD40 extracellular domain expressed with a C-terminal myc-myc-hexahistidine (SEQ ID NO: 1114) (hCD40-MMH; SEQ ID NO: 53) was first captured onto anti-Penta-His (SEQ ID NO: 1113) antibody coated Octet biosensor tips (Fortebio Inc, # 18-5122) by submerging the biosensor tips in wells containing 10 µg/mL solution of the hCD40-MMH for 90 seconds. The antigen captured biosensor tips were then saturated

with a first anti-CD40 monoclonal antibody (subsequently referred to as "mAb-1") by dipping into wells containing 50 µg/mL solution of mAb-1 for 4 minutes. The biosensor tips were then subsequently dipped into wells containing 50 µg/mL solution of a second anti-CD40 monoclonal antibody (subsequently referred to as "mAb-2") for 3 minutes. The biosensor tips were washed in HBS-EBT buffer in between every step of the experiment. The real-time binding response was monitored and the binding response at the end of every step was recorded. The response of mAb-2 binding to hCD40-MMH pre-complexed with mAb-1 was compared to the binding response hCD40-MMH alone (sample of isotype control), and if pre-bound mAb-1 reduced binding of mAb-2 by more than 50%, mAb-1 was considered to be a competitor to mAb-2.

[01578] Competitors of each antibody tested are summarized in **Table 13** below. Parental antibodies 21519P2 and 21520P2 were found to compete with each other, but not with 30027P2, for binding to hCD40-MMH.

Table 13: Cross-competition between different anti-CD40 monoclonal antibodies for binding to hCD40-MMH

Prebound mAb-1	**mAb-2 blocked by mAb-1 (> 50%)**
21519P2	21519P2
	21520P2
21520P2	21520P2
	21519P2
30027P2	30027P2
REGN11209	REGN11209
	21519P2
	21520P2

Example 4: ELISA Assay to Assess Blocking Activity of Anti-CD40xCD40 Bispecific Antibodies

[01579] An ELISA-based blocking assay was developed to determine the ability of C40xCD40 bispecific antibodies to block the binding of the hCD40 monomer to plate-coated hCD40L. The recombinant human CD40-mmH protein (hCD40-MMH; REGN3094; SEQ ID NO: 53) used in the experiments comprises a portion of the human CD40 extracellular domain (amino acids

P20-R193) fused to 2xMyc peptide and 6xhistadine (SEQ ID NO: 1110) at the C-terminus of human CD40, and the human CD40L (accession # NM_000074.2) with amino acids E108-L261 of the extracellular domain with 9x His-2x(SGGG)-IGER at the N-terminus (9His-hCD40L) was commercially obtained from Biolegend.

[01580] In the blocking assay, 9His-hCD40L was passively absorbed at a concentration of 5 µg/mL in PBS on a 96-well microtiter plate overnight at 4°C. Nonspecific binding sites were subsequently blocked using a 0.5% (w/v) solution of BSA in PBS. In a separate 96-well microtiter plate, a fixed amount of 40 nM hCD40-mmH was pre-mixed with one of the following antibodies, at concentrations ranging from 977 pM to 1 µM in PBS+0.5% BSA: (1) CD40xCD40 bispecific antibodies (REGN16431, REGN16432, REGN16634, and REGN16335); (2) parental CD40 mAbs (bivalent antibodies comprising 2 fragment antigen-binding [Fab] arms identical to one of anti-CD40 Fab of CD40xCD40 antibodies); (3) CD40xIrrelevant antibodies (bivalent antibodies that incorporate one Fab arm identical to one of anti-CD40 Fab of CD40xCD40 antibodies and another Fab arm specific to an irrelevant antigen); and (4) human IgG4 with Fc mutation isotype control antibodies (REGN7540 and REGN4513). The fixed concentration of hCD40-mmH was selected to be near the concentration (EC_{50} value) that generated 50% of the maximal binding to the plate-adhered 9His-hCD40L. After one-hour incubation, the antibody-antigen complexes were transferred to the microtiter plate coated with 9His-hCD40L. After one hour incubation at room temperature, the plates were washed, and plate-bound hCD40-mmH protein was detected with horseradish peroxidase (HRP) conjugated goat anti-c-Myc antibody. The plates were then developed using TMB substrate solution (BD Biosciences) according to the manufacturer's recommended procedure and the absorbance at 450nm (OD_{450}) was measured on a SpectraMax i3x plate reader.

[01581] Binding data were analyzed using a sigmoidal (four-parameter logistic) dose-response model with GraphPad Prism™ software. The IC_{50} value, defined as the concentration of antibody required to block 50% of 40 nM hCD40-mmH binding to plate-coated 9His-hCD40L, was determined to indicate blocking potency. The percent blocking of tested antibodies at the highest tested concentration (1µM) was calculated based on the formula shown below:

$$\% \text{ Blocking} = 100 - \left(\frac{[\text{Experimental Signal}_{(300\text{nM Ab})} - \text{Background Signal}_{(\text{buffer})}]}{[\text{Maximum Signal}_{(1\text{nM hCD40-mFc alone})} - \text{Background Signal}_{(\text{buffer})}]}\right) \times 100$$

where the maximum signal was the interpolated binding signal for 40 nM hCD40-mmH from the hCD40-mmH concentration-response curve. Antibodies that blocked binding of hCD40 greater than 50% were classified as blockers. Antibodies that blocked binding equal or less than 50% were classified as non-blockers. IC_{50} values for nonblockers were not determined.

Results

[01582] The ability of CD40xCD40 bispecific antibodies to block human CD40 monomer binding to plate-coated human CD40L was assessed using a sandwich ELISA-based blocking assay. The results are shown in **Table 14**. As shown in **Table 14**, each of the CD40xCD40 bispecific antibodies REGN16431, REGN16432, REGN16334, and REGN16335 displayed concentration-dependent blocking of hCD40 binding to hCD40L with 93% to 98% blocking at the highest antibody concentration tested (1 μM). The IC_{50} values for these bispecific antibodies are similar around 32 nM. The four parental anti-CD40 antibodies (H4sH21519P2, H4sH21520P2, REGN17288, REGN17544) displayed maximum blocking ranging from 91% to 94% and IC_{50} values from 52 nM to 71 nM. Four CD40xIrrelevant antibodies (REGN17551, REGN17552, REGN17548, RENG17549) also inhibited hCD40 binding to hCD40L with blocking ranging from 83% to 87%. Two parental CD40 antibodies (H4sH30027P2 and REGN17289) and two CD40xIrrelevant antibodies (REGN17553 and REGN17550) showed minimum blocking activity around 10% and were classified as non-blockers. In this experiment the two human IgG4 with Fc mutation isotype control antibodies (REGN7540, REGN4513) showed no blocking activity, as expected.

Table 14: Summary of CD40 antibodies blocking human CD40 monomer binding to human CD40L

Antibody ID	Antibody format	mAb blocking 40nM hCD40-mmH binding to 9His-hCD40L	
		IC_{50} (M)	% Blocking at 1 M mAb
REGN16431	CD40xCD40	3.3E-08	93
REGN16432	CD40xCD40	3.2E-08	95
REGN16334	CD40xCD40	3.2E-08	98
REGN16335	CD40xCD40	3.2E-08	96
H4sH21519P2	Parental CD40	6.1E-08	94
H4sH21520P2	Parental CD40	6.2E-08	94
H4sH30027P2	Parental CD40	NBL	10
REGN17288	Parental CD40	5.2E-08	94
REGN17544	Parental CD40	7.1E-08	91
REGN17289	Parental CD40	NBL	10
REGN17551	CD40xIrrelevant	ND	87
REGN17552	CD40xIrrelevant	ND	84
REGN17553	CD40xIrrelevant	NBL	10
REGN17548	CD40xIrrelevant	ND	86
REGN17549	CD40xIrrelevant	ND	83
REGN17550	CD40xIrrelevant	NBL	10

REGN7540	Human IgG4 with Fc mutation isotype control 1	NBL	-6
REGN4513	Human IgG4 with Fc mutation isotype control 2	NBL	0

NBL: Non-blocking (% blocking is 50% or less)
ND: Not determined (no sigmoidal curve fit observed to calculate IC_{50} values)

Example 5: Anti-CD40xCD40 Bispecific Antibody Binding to Cell-Surface CD40 as Measured by Flow Cytometry

[01583] Flow cytometry was used to assess the ability of anti-CD40xCD40 bispecific antibodies to bind human CD40 (hCD40) or *Macaca fascicularis* CD40 (mfCD40) expressing cells. Human embryonic kidney 293 (HEK293) cells stably expressing luciferase reporter gene under the control of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and enhanced green fluorescent protein (HEK293/D9) were engineered to express hCD40 (accession #P25942-1) or mfCD40 (accession #XP_005569274.1) by transfecting the cells with neomycin resistant pRG984 plasmid encoding full-length hCD40 (amino acids M1-Q277, HEK293/D9/hCD40), or neomycin resistant pRG984 plasmid encoding full-length mfCD40 (amino acids M1-Q282, HEK293/D9/mfCD40). Ramos 2G6.4C10 cells were utilized to evaluate the binding of anti-CD40 antibodies to hCD40 endogenously expressed on the cell surface. CD40 negative HEK293/D9 cells that showed no detectable expression of CD40 by flow cytometry with a commercial anti-CD40 antibody were included as a background binding control.

[01584] Experiments were carried out according to the following procedure: HEK293/D9/hCD40, HEK293/D9/mfCD40 or HEK293/D9 cells were rinsed once in 1xPBS buffer without Ca^{2+}/Mg^{2+} and incubated for 10 minutes at 37°C with Enzyme Free Cell Dissociation Solution to detach cells from flask. The dissociated cells or Ramos 2G6.4G10 suspension cells were washed with 1xPBS and counted with Cellometer™ Auto T4 cell counter (Nexcelom Bioscience, Lawrence, MA). Cells were then resuspended to $1x10^7$ per mL in 1xPBS and separately stained with 2.5 µM of CellTrace™ reagents (Invitrogen, Carlsbad, CA) for 20 minutes at room temperature (RT) to generate a unique fluorescence signature for each cell line (CellTrace™ CFSE for Ramos 2G6.4C10 cells, CellTrace™ Violet for HEK293/D9/mfCD40 cells, CellTrace™ Yellow for HEK293/D9 cells, and HEK293/D9/hCD40 cells were unstained). CellTrace™ labeling reaction was stopped by adding FBS to a final concentration of 25% in 1xPBS followed by a 5-minute incubation at room temperature to quench unbound dye in

solution. Cells were washed with 1xPBS and equal numbers of each of the four cell lines, stained and unstained, were mixed in a ratio of 1:1:1:1 for multiplexing. Approximately $2x10^5$ cells per well were seeded onto 96-well Corning plates and stained with LIVE/DEAD™ Fixable Near-IR (Thermo Fisher Scientific, Waltham, MA) in 1xPBS for 20 minutes at 4°C following a manufacturer's recommended procedure to discriminate live and dead cells. Cells were washed with 2% FBS (w/v) in 1xPBS (flow cytometry staining buffer) by centrifugation with benchtop Centrifuge 5810R (Eppendorf®, Hamburg, Germany). Cells were incubated for 30 minutes at 4°C with serial dilutions of following antibodies ranging from 1.7 pM to 100 nM in flow cytometry staining buffer: (1) anti-CD40xCD40 bispecific antibodies, or (2) parental anti-CD40 antibodies (bivalent antibodies comprising 2 fragment antigen-binding [Fab] arms identical to one of the two anti-CD40 Fab of bispecific anti-CD40xCD40 antibodies), or (3) anti-CD40xIrrelevant antibodies (bivalent antibodies that incorporate one Fab arm identical to one of anti-CD40 Fab of anti-CD40xCD40 antibodies and another Fab arm specific to an irrelevant antigen, i.e. birch pollen main allergen Bet v1), or (4) human IgG4 isotype control antibodies with Fc mutation. After washing, cell bound antibodies were detected with 2.5 µg/ml Allophycocyanin (APC)-conjugated goat anti-human IgG antibody specific for the Fcγ fragment (Jackson Immunoresearch, West Grove, PA) for 30 minutes at 4°C. Cells were washed and subsequently fixed with 50% solution of Cytofix™ Fixation Buffer (BD, Franklin Lakes, NJ) in flow cytometry staining buffer for 20 minutes at room temperature. Cells were washed and resuspended in flow cytometry staining buffer and stored at 4°C for downstream flow cytometry analysis.

[01585] Acquisition of fluorescence signals were recorded on the ZE5 Cell Analyzer (Bio-Rad, Hercules, CA) according to the manufacturer's recommended procedure and flow cytometry data analysis was performed using the open-source R packages flowCore, flowStats, flowDensity, ggCyto, and flowAI. Multiplexed samples were deconvoluted and individual cell populations were identified based on their unique CellTrace™ fluorescence signature. APC Median Fluorescence intensity (MFI) was recorded to indicate the binding intensity of each antibody over a range of concentrations. Antibodies with MFI greater than 1500 at the highest tested concentration (100 nM) were classified as specific binders. In addition, direct binding signals (APC MFI) were analyzed as a function of the antibody concentration and data were fitted with a sigmoidal (four-parameter logistic) dose-response model using GraphPad Prism™ software. The EC_{50} value, defined as the concentration of antibody that yields 50% of the maximal binding, was determined and used as an indicator of antibody binding potency. EC_{50} values were reported only for specific binders.

Results

[01586] The ability of anti-CD40xCD40 bispecific antibodies to bind specifically cells expressing human or monkey CD40 was assessed by flow cytometry. The experimental results are summarized in **Table 15** below.

[01587] The four anti-CD40xCD40 bispecific antibodies (REGN16431, REGN16432, REGN16334, and REGN16335) displayed concentration-dependent specific binding to hCD40 expressed on HEK293/D9/hCD40 or Ramos 2G6.4C10 cells with MFI values ranging from 28,932 to 30,315 at the highest concentration tested (100 nM) and EC_{50} values of 1.5 nM to 2.0 nM on HEK293/D9/hCD40 cells, or with MFI values from 3,748 to 3,852 and EC50 values of 1.0 nM to 2.0 nM on Ramos 2G6.4C10 cells. The four bispecific antibodies similarly displayed specific binding to mfCD40 expressed on HEK293/D9/mfCD40 cells with MFI values ranging from 41,714 to 48,653 and EC_{50} values of 2.1 nM to 9.1 nM.

[01588] Six parental anti-CD40 antibodies (H4sH21519P2, H4sH21520P2, H4sH30027P2, REGN17288, REGN17544, and REGN17289) displayed specific binding to HEK293/D9/hCD40 or Ramos 2G6.4C10 cells with MFI values ranging from 20,213 to 20,911 and EC_{50} values of 0.72 nM to 1.3 nM on HEK293/D9/hCD40 cells, or with MFI values ranging from 2,408 to 2,664 and EC_{50} values of 0.45 nM to 1.5 nM on Ramos 2G6.4C10 cells. All parental anti-CD40 antibodies showed specific binding to HEK293/D9/mfCD40 cells with MFI values ranging from 11,539 to 33,930 and EC_{50} values of 1.0 nM to 10 nM.

[01589] Six anti-CD40xIrrelevant antibodies (REGN17551, REGN17552, REGN17553, REGN17548, REGN17549, and REGN17550) displayed specific binding to HEK293/D9/hCD40 or Ramos 2G6.4C10 cells with MFI values ranging from 21,394 to 24,591 and EC_{50} values of 1.1 nM to 8.2 nM on HEK293/D9/hCD40 cells, or with MFI values ranging from 1,833 to 3,140 on Ramos 2G6.4C10 cells. Four anti-CD40xIrrelevant antibodies (REGN17552, REGN17553, REGN17549, and REGN17550) displayed specific binding to HEK293/D9/mfCD40 cells with MFI values ranging from 4,719 to 39,448, but two anti-CD40xIrrelevant antibodies (REGN17551 and REGN17548) did not specifically bind to mfCD40 on HEK293/D9/mfCD40 cells.

[01590] All tested anti-CD40 antibodies did not bind to the negative control HEK293/D9 cells: binding signals were below 950 MFI. As expected, no detectable cell-surface binding was observed for two hIgG4 with Fc mutation isotype control antibodies (REGN7540 and REGN4513) up to the highest antibody concentration tested (100 nM).

Table 15: Summary of anti-CD40 antibody binding to human or monkey CD40 expressed on the cell surface

Antibody ID	Antibody Format	HEK293/D9/hCD40		Ramos 2G6.4C10 (hCD40 positive)		HEK293/D9/mfCD40		HEK293/D9 (CD40 negative)	
		EC_{50} (M)	MFI at 100 nM	EC_{50} (M)	MFI at 100 nM	EC_{50} (M)	MFI at 100 nM	EC_{50} (M)	MFI at 100 nM
REGN16431	CD40xCD40	1.9E-09	29464	1.9E-09	3851	8.4E-09	43145	ND	929
REGN16432	CD40xCD40	1.5E-09	30315	1.1E-09	3852	2.1E-09	48653	ND	949
REGN16334	CD40xCD40	2.0E-09	29042	2.0E-09	3759	9.1E-09	41714	ND	940
REGN16335	CD40xCD40	1.6E-09	28932	1.0E-09	3748	2.4E-09	47289	ND	883
H4sH21519P2	Parental CD40	1.3E-09	20213	1.5E-09	2408	1.0E-08	11539	ND	434
H4sH21520P2	Parental CD40	8.2E-10	20681	8.0E-10	2446	3.7E-09	24090	ND	558
H4sH30027P2	Parental CD40	7.2E-10	20911	4.5E-10	2623	1.0E-09	33930	ND	650
REGN17288	Parental CD40	1.2E-09	20334	1.3E-09	2422	9.2E-09	11781	ND	488
REGN17544	Parental CD40	9.8E-10	20511	8.7E-10	2445	4.3E-09	23174	ND	599
REGN17289	Parental CD40	7.6E-10	20472	4.7E-10	2664	1.1E-09	32927	ND	618
REGN17551	CD40xIrrelevant	7.5E-09	23314	INC	2725	ND	1364	ND	328
REGN17552	CD40xIrrelevant	7.0E-09	21394	INC	1833	INC	4719	ND	433
REGN17553	CD40xIrrelevant	1.1E-09	24591	9.5E-10	3140	1.4E-9	39448	ND	822
REGN17548	CD40xIrrelevant	8.2E-09	23974	INC	2732	ND	1126	ND	311
REGN17549	CD40xIrrelevant	7.5E-09	22619	INC	2004	INC	5633	ND	471
REGN17550	CD40xIrrelevant	1.2E-09	24376	8.7E-10	3026	1.6E-09	39131	ND	776
REGN7540	Human IgG4 with Fc mutation Isotype control 1	ND	218	ND	74	ND	352	ND	181
REGN4513	Human IgG4 with Fc mutation Isotype control 2	ND	24	ND	42	ND	22	ND	21

MFI, median fluorescence intensity; INC, inconclusive; ND, not determined. INC is applied if concentration-dependent binding was detected, but no top plateau was reached in the concentraton range tested, and an EC_{50} therefore could not be calculated. If MFI values were less than or equal to 1500 and specifidc binding was not detected, EC_{50} was not calculated and ND was applied.

Example 6: Bioassay to Assess Regulation of CD40 Signaling by Anti-CD40xCD40 Bispecific Antibodies

[01591] CD40 is a member of the tumor necrosis factor receptor superfamily (TNFRSF) that activates the immune system in response to the binding of its ligand, CD40L. To evaluate regulation of CD40 signaling, a bioassay was developed to quantitatively assess receptor activation by measuring gene expression downstream of the nuclear translocation of NFκB (nuclear factor κB). The luciferase-based reporter assay was engineered in three different human cell lines (Ramos.2G6.4C10, Raji, and THP-1) that endogenously express CD40. Cells were transduced with NFκB-luciferase reporter lentivirus (QIAGEN CLS-013L-8) and stable reporter cell lines were selected and maintained in media containing 1 µg/ml of puromycin.

[01592] For the bioassay, cells were seeded at 20,000 cells/well into 96-well plates in assay media (RPMI-1640 with 10%FBS, pen/strep/glut). Antibodies were then serially diluted in assay media at 1:3 to final concentrations ranging from 100 nM to 1.7 pM (with an additional condition without test molecule) and added to the cells along with or without a constant concentration of human CD40L (500 pM, 900 pM, or 10 nM for Ramos, Raji, or THP1 reporter cells, respectively). To obtain a range of activation, hCD40L was serially diluted 1:3 to final concentrations ranging from 100 nM to 1.7 pM (with an additional condition without ligand) and added to cells. After 5 hours of incubation at 37°C / 5% CO_2, luciferase activity was detected on an Envision multilabel plate reader (PerkinElmer) after the addition of ONE-Glo™ (Promega) reagent. All conditions were tested in duplicate.

[01593] The EC_{50} or IC_{50} values were determined with GraphPad Prism™ software using nonlinear regression (4-parameter logistics). The percentage of inhibition was calculated based on the relative luminescence unit (RLU) values using the equation:

$$\%\,\text{Activation} = 100\% \times \frac{RLU_{Antibody\ Maximum} - RLU_{Background}}{RLU_{Ligand\ Maximum} - RLU_{Background}}$$

$$\%\,\text{Inhibition} = 100\% \times \frac{RLU_{Ligand\ Constant} - RLU_{Antibody\ Minimum}}{RLU_{Ligand\ Constant} - RLU_{Background}}$$

[01594] "$RLU_{\text{Antibody Maximum}}$" and "$RLU_{\text{Antibody minimum}}$" are the maximum and minimum luminescence value achieved with antibody. "$RLU_{\text{Ligand Maximum}}$" and "$RLU_{\text{Ligand constant}}$" are the values achieved by maximum and constant concentration of CD40L. "$RLU_{\text{Background}}$" is the value without any CD40L. For antibodies that showed potentiation in the presence of CD40L, "$RLU_{\text{Antibody Maximum}}$" was used to calculate % inhibition leading to negative inhibition values.

Results

[01595] As shown in **Table 16**, anti-CD40xCD40 bispecific antibodies REGN16431, REGN16432, REGN16334 and REGN16335 showed minimal activation ranging from 4 to 6% without CD40L and inhibition ranging from 90 to 94% with IC_{50}s of 38.6 – 85.4 pM with 500 pM CD40L in Ramos.2G6.4C10/NFκB-luc cells. Anti-CD40 bivalent antibodies and anti-CD40 x Irrel. (Irrelevant, Non-CD40 target) antibodies showed activation ranging from 4 to 49% without CD40L and inhibition ranging from 28 to 95% with 500 pM CD40L. Four antibodies showed potentiation of signaling, inhibition ranging from -110 to -142% in the presence of CD40L in Ramos bioassay.

[01596] As shown in **Table 17**, anti-CD40xCD40 bispecific antibodies REGN16431, REGN16432, REGN16334 and REGN16335 showed minimal activation ranging from 5 to 13% without CD40L and inhibition ranging from 68 to 113% with IC_{50}s of 49.4 – 107 pM with 900 pM CD40L in Raji/NFκB-luc cells. Anti-CD40 bivalent antibodies and anti-CD40 x Irrel. antibodies showed activation ranging from 7 to 25% without CD40L and inhibition ranging from 33 to 92% with 900 pM CD40L in Raji bioassay.

[01597] As shown in **Table 18**, anti-CD40xCD40 bispecific antibodies REGN16431, REGN16432, REGN16334 and REGN16335 showed minimal activation ranging from 1 to 6% without CD40L and inhibition ranging from 97 to 98% with IC_{50}s of 148 – 553 pM with 10 nM CD40L in THP-1/NFκB-luc cells. Anti-CD40 bivalent antibodies and anti-CD40 x Irrel. antibodies showed activation ranging from 0 to 5% without CD40L and inhibition ranging from 54 to 101% with 10 nM CD40L. Four antibodies showed potentiation of signaling, inhibition ranging from -45 to -92%, in the presence of CD40L in THP-1 bioassay.

[01598] Control mAb1, Control mAb2 and Control mAb3, irrelevant human IgG antibodies, showed little to no activation (0 – 13%) without CD40L and inhibition (3 – 23%) with CD40L in all cells. CD40L showed activation of signaling with EC_{50}s of 436 pM, 691 pM and 1.47 nM in Ramos.2G6.4C10/NFκB-luc, Raji//NFκB-luc, and THP-1/NFκB-luc cells, respectively.

Table 16: Anti-CD40 x CD40 bispecific antibody regulation of CD40 signaling in the presence or absence of human CD40L using Ramos.2G6.4C10/NFκB-luc cells

Antibody	Specificity	Regulation with No Ligand		Regulation with 500 pM hCD40L	
		EC50 [M]	Max % activation	IC50/EC50 [M]	Max % inhibition
REGN16431	CD40 X CD40 (21519 X 21520)	No Activation	6	8.54E-11	90

Antibody	Specificity	Regulation with No Ligand		Regulation with 500 pM hCD40L	
		EC50 [M]	Max % activation	IC50/EC50 [M]	Max % inhibition
REGN16432	CD40 X CD40 (30027 X 21520)	No Activation	4	4.92E-11	94
REGN16334	CD40 X CD40 (21519 X 21520)	No Activation	6	6.93E-11	91
REGN16335	CD40 X CD40 (30027 X 21520)	No Activation	5	3.86E-11	93
H4sH21519P2	CD40 (21519)	No Activation	13	3.09E-11	88
H4sH21520P2	CD40 (21520)	>1.00E-08	49	8.06E-11#	63
H4sH30027P2	CD40 (30027)	No Activation	8	8.14E-12*	-130
REGN17288	CD40 (21519)	No Activation	6	4.07E-11	88
REGN17544	CD40 (21520)	No Activation	10	1.89E-10	77
REGN17289	CD40 (30027)	No Activation	4	7.51E-12*	-133
REGN17548	CD40 X Irrel. (21519 X Irrel.)	No Activation	4	1.05E-08	95
REGN17549	CD40 X Irrel. (21520 X Irrel.)	>1.00E-08	25	>1.00E-08	28
REGN17550	CD40 X Irrel. (30027 X Irrel.)	No Activation	5	2.45E-11*	-142
REGN17551	CD40 X Irrel. (21519 X Irrel.)	No Activation	5	7.29E-09	95
REGN17552	CD40 X Irrel. (21520X Irrel.)	>1.00E-08	20	>1.00E-08	51
REGN17553	CD40 X Irrel. (30027 X Irrel.)	No Activation	4	2.63E-11*	-110
Control Mab1	Irrel.	No Activation	4	No Inhibition	5
Control mAb2	Irrel.	No Activation	4	No Inhibition	3
Control mAb3	Irrel.	No Activation	2	No Inhibition	12

* Values represent EC_{50} calculations in the presence of CD40L. All other values are IC_{50}s.
# IC_{50} values was obtained by excluding RLU values from conditions containing three highest concentrations of antibody due to hook effect.

Table 17: Anti-CD40 x CD40 bispecific antibody regulation of CD40 signaling in the presence or absence of human CD40L using Raji/NFκB-luc cells

Antibody	Specificity	Regulation with No Ligand	Regulation with 900pM hCD40L

		EC50 [M]	Max % activation	IC50 [M]	Max % inhibition
REGN16431	CD40 X CD40 (21519 X 21520)	No Activation	13	1.07E-10	82
REGN16432	CD40 X CD40 (30027 X 21520)	No Activation	5	1.02E-10	68
REGN16334	CD40 X CD40 (21519 X 21520)	No Activation	13	5.76E-11	113
REGN16335	CD40 X CD40 (30027 X 21520)	No Activation	9	4.94E-11	102
H4sH21519P2	CD40 (21519)	No Activation	15	6.05E-11	92
H4sH21520P2	CD40 (21520)	>1.00E-07	25	7.70E-11	81
H4sH30027P2	CD40 (30027)	No Activation	9	8.95E-12	67
REGN17288	CD40 (21519)	No Activation	14	4.28E-11	90
REGN17544	CD40 (21520)	No Activation	11	1.35E-10	81
REGN17289	CD40 (30027)	No Activation	10	2.72E-11	55
REGN17548	CD40 X Irrel. (21519 X Irrel.)	No Activation	9	>1.00E-08	74
REGN17549	CD40 X Irrel. (21520 X Irrel.)	No Activation	11	>1.00E-08	52
REGN17550	CD40 X Irrel. (30027 X Irrel.)	No Activation	14	2.99E-10	33
REGN17551	CD40 X Irrel. (21519 X Irrel.)	No Activation	14	>1.00E-08	58
REGN17552	CD40 X Irrel. (21520X Irrel.)	No Activation	14	>1.00E-08	56
REGN17553	CD40 X Irrel. (30027 X Irrel.)	No Activation	7	1.39E-10	37
Control Mab1	Irrel.	No Activation	6	No Inhibition	23
Control mAb2	Irrel.	No Activation	9	No Inhibition	19
Control mAb3	Irrel.	No Activation	13	No Inhibition	16

Table 18: Anti-CD40 x CD40 bispecific antibody regulation of CD40 signaling in the presence or absence of human CD40L using THP-1/NFκB-luc cells

Antibody	Specificity	Regulation with No Ligand		Regulation with 10nM hCD40L	
		EC50 [M]	Max % activation	IC50/EC50 [M]	Max % inhibition
REGN16431	CD40 X CD40 (21519 X 21520)	No Activation	2	2.87E-10	98

Antibody	Specificity	Regulation with No Ligand		Regulation with 10nM hCD40L	
		EC50 [M]	Max % activation	IC50/EC50 [M]	Max % inhibition
REGN16432	CD40 X CD40 (30027 X 21520)	No Activation	6	1.48E-10	97
REGN16334	CD40 X CD40 (21519 X 21520)	No Activation	1	5.53E-10	98
REGN16335	CD40 X CD40 (30027 X 21520)	No Activation	3	2.21E-10	98
H4sH21519P2	CD40 (21519)	No Activation	5	2.76E-10	99
H4sH21520P2	CD40 (21520)	No Activation	1	4.37E-10	97
H4sH30027P2	CD40 (30027)	No Activation	2	2.51E-12*	-61
REGN17288	CD40 (21519)	No Activation	0	3.34E-10	98
REGN17544	CD40 (21520)	No Activation	4	1.13E-09	96
REGN17289	CD40 (30027)	No Activation	1	1.60E-11*	-92
REGN17548	CD40 X Irrel. (21519 X Irrel.)	No Activation	2	1.51E-08	97
REGN17549	CD40 X Irrel. (21520 X Irrel.)	No Activation	1	>1.00E-08	54
REGN17550	CD40 X Irrel. (30027 X Irrel.)	No Activation	1	4.64E-11*	-74
REGN17551	CD40 X Irrel. (21519 X Irrel.)	No Activation	1	4.55E-09	101
REGN17552	CD40 X Irrel. (21520X Irrel.)	No Activation	3	>1.00E-08	83
REGN17553	CD40 X Irrel. (30027 X Irrel.)	No Activation	1	Not Determined*	-45
Control Mab1	Irrel.	No Activation	0	No Inhibition	13
Control mAb2	Irrel.	No Activation	1	No Inhibition	4
Control mAb3	Irrel.	No Activation	2	No Inhibition	5

* Values represent EC_{50} calculations in the presence of CD40L. EC_{50} value was not determined where best-fit value was not found. All other values are IC_{50}s.

Example 7: *In Vitro* CD40L Blocking Activity by Anti-CD40xCD40 Bispecific Antibodies

B Cell Assay #1

[01599] To determine the efficacy of anti-CD40xCD40 bispecific antibodies to block stimulation by CD40L, IL-6, IL-10, and TNFα cytokine production was quantified in primary human B cell cultures treated with antibodies in the presence of soluble CD40L. B cells were plated at $2x10^5$ cells per well in a 96 U-bottom plate in RPMI 1640 media with 15% FBS and 1x penicillin-streptomycin. Anti-CD40xCD40 bispecific antibodies were added to cells simultaneously in the

presence of a constant dose of IL-4 (10 pM) and CD40L (500 nM). A dose response of CD40L with a constant dose of IL-4 (10 pM) was included as a control. Cells were cultured for 3 days at 37°C, and cell culture supernatant was collected for analysis.

[01600] Cytokine levels in supernatant were analyzed using the MSD V-PLEX proinflammatory panel 1. MSD V-PELX assay was performed according to the manufacturer's instruction using cell culture supernatant diluted 1:2. MSD plates were read using an MESO QuickPlex Sq 120MM instrument and MSD Discovery Workbench software. Data analysis was performed using Graphpad Prism software. The data points obtained were transformed using an X=Log(X) equation, and the transformed data were subjected to a linear regression analysis and fitted into a sigmoidal dose response curve. IC_{50}s were derived from this analysis.

Results

[01601] All four antibodies tested (REGN16334, REGN16335, REGN16431, and REGN16432) blocked IL-6 (**Figures 1A, 1B, and 1C**), IL-10 (**Figures 2A, 2B, and 2C**), and TNFα (**Figures 3A, 3B, and 3C**) production from primary human B cells from three donors in response to stimulation with CD40L. IC_{50} values of antibodies and COMP11209 (a comparator anti-CD40 antibody) are shown in **Table 19** (IL-6), **Table 20** (IL-10), and **Table 21** (TNFα). The percent max blockade was calculated with the highest dose of REGN16334, REGN16335, REGN16431, and REGN16432, relative to the average cytokine levels in cells treated with no antibody.

Table 19: Effect of anti-CD40xCD40 bispecific antibodies on human B cell IL-6 production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	Donor 1 % max blockade relative to no mAb	IC_{50} Donor 2	Donor 2 % max blockade relative to no mAb	IC_{50} Donor 3	Donor 3 % max blockade relative to no mAb
REGN16334	4.400e-010	84.49%	2.474e-010	92.00%	2.474e-010	92.00%
REGN16335	1.281e-010	83.22%	4.579e-011	91.36%	4.579e-011	91.36%
REGN16431	4.488e-010	84.05%	2.051e-010	92.66%	2.051e-010	92.66%
REGN16432	1.081e-010	83.54%	5.866e-011	92.04%	5.866e-011	92.04%
COMP11209	4.341e-010	84.20%	2.444e-010	91.32%	2.444e-010	91.32%

Table 20: Effect of anti-CD40xCD40 bispecific antibodies on human B cell IL-10 production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	Donor 1 % max blockade relative to no mAb	IC_{50} Donor 2	Donor 2 % max blockade relative to no mAb	IC_{50} Donor 3	Donor 3 % max blockade relative to no mAb
REGN16334	6.721e-010	74.23%	2.759e-010	91.42%	6.466e-010	92.42%
REGN16335	1.971e-010	78.54%	6.116e-011	93.60%	1.104e-010	89.80%
REGN16431	8.224e-010	80.68%	2.242e-010	86.87%	~ 5.481e-010	89.29%
REGN16432	1.767e-010	81.55%	9.896e-011	94.47%	9.371e-011	90.62%
COMP11209	3.894e-010	84.09%	2.392e-010	91.67%	3.399e-010	91.43%

Table 21: Effect of anti-CD40xCD40 bispecific antibodies on human B cell TNFα production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	Donor 1 % max blockade relative to no mAb	IC_{50} Donor 2	Donor 2 % max blockade relative to no mAb	IC_{50} Donor 3	Donor 3 % max blockade relative to no mAb
REGN16334	7.374e-010	44.05%	3.207e-010	63.52%	3.047e-010	68.51%
REGN16335	2.888e-011	44.98%	2.906e-011	64.66%	5.743e-011	61.62%
REGN16431	3.989e-010	44.70%	4.395e-010	74.13%	4.711e-010	70.43%
REGN16432	3.291e-011	53.54%	5.596e-011	68.40%	8.796e-011	69.14%
COMP11209	3.667e-010	53.86%	2.799e-010	71.40%	2.838e-010	73.91%

B Cell Assay #2

[01602] To determine the efficacy of CD40xCD40 bispecific antibodies to block stimulation by CD40L, IL-6, IL-10, and TNFα cytokine production was quantified in primary human B cell cultures treated with antibodies in the presence of soluble CD40L. B cells were plated at $2x10^5$ cells per well in a 96 U-bottom plate in RPMI 1640 media with 15% FBS and 1x penicillin-streptomycin and incubated with CD40xCD40 bispecific antibodies for 30 minutes at 37°C. Following antibody incubation, a constant dose of IL-4 (10 pM) and CD40L (500 nM) was added to the B cell cultures in the presence of the CD40xCD40 bispecific antibodies. A dose response of CD40L with a constant dose of IL-4 (10 pM) was included as a control. In parallel, to quantify the agonistic activity of CD40xCD40 bispecific antibodies, B cells were incubated with antibodies in the presence of a constant dose of IL4 (10 pM) without CD40L. Cells were cultured for 3 days at 37°C, and cell culture supernatant was collected for analysis.

[01603] Cytokine levels in supernatant were analyzed using the MSD V-PLEX proinflammatory panel 1. MSD V-PELX assay was performed according to the manufacturer's instruction using cell culture supernatant diluted 1:2. MSD plates were read using an MESO QuickPlex Sq 120MM instrument and MSD Discovery Workbench software. Data analysis was performed using Graphpad Prism software. The data points obtained were transformed using an X=Log(X) equation, and the transformed data were subjected to a linear regression analysis and fitted into a sigmoidal dose response curve. IC_{50}s were derived from this analysis.

Results

[01604] All three CD40xCD40 bispecific antibodies tested (REGN16334, REGN16335, and REGN20484) blocked IL6 (Fig. 1D and 1E), IL10 (Fig. 2D and 2E), and TNFα (Fig. 3D and 3E) cytokine production from primary human B cells from two donors in response to stimulation with CD40L. IC_{50} values of antibodies and COMP11209 are shown in **Tables 22-24**. The percent max blockade was calculated with the highest dose of REGN16334, REGN16335, and REGN20484, relative to the average cytokine levels in cells treated with no antibody. Analysis of agonistic activity of antibodies REGN16334, REGN16335, and REGN20484 showed induction of the cytokine IL6 within a range comparable to cells treated with IL4 only (no antibody) in both donors (Fig. 3F and 3G).

Table 22: Effect of CD40xCD40 bispecific antibodies on human B cell IL-6 production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	Donor 1 % max blockade relative to no mAb	IC_{50} Donor 2	Donor 2 % max blockade relative to no mAb
REGN16334	3.505e-010	88.89%	3.753e-010	89.15%
REGN16335	5.645e-012	88.41%	4.403e-011	87.04%
REGN20484	6.741e-011	88.96%	6.758e-011	88.10%
COMP11209	2.534e-010	88.59%	3.806e-010	88.30%

Table 23: Effect of CD40xCD40 bispecific antibodies on human B cell IL-10 production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	Donor 1 % max blockade relative to no mAb	IC_{50} Donor 2	Donor 2 % max blockade relative to no mAb
REGN16334	3.874e-010	87.68%	3.747e-010	89.92%
REGN16335	1.413e-011	88.54%	5.451e-011	87.75%
REGN20484	9.206e-011	87.07%	8.723e-011	90.92%

COMP11209	2.767e-010	88.08%	3.360e-010	90.48%

Table 24: Effect of CD40xCD40 bispecific antibodies on human B cell TNFα production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	Donor 1 % max blockade relative to no mAb	IC_{50} Donor 2	Donor 2 % max blockade relative to no mAb
REGN16334	2.176e-010	62.82%	3.776e-010	51.15%
REGN16335	4.396e-011	62.40%	~ 2.967e-016	52.52%
REGN20484	6.632e-011	61.87%	4.573e-011	52.27%
COMP11209	2.364e-010	62.03%	4.054e-010	50.57%

Dendritic Cell Assay

[01605] To determine the efficacy of anti-CD40xCD40 bispecific antibodies to block stimulation by CD40L, IL-12/IL-23p40 cytokine production was quantified in primary human monocyte derived dendritic cell (MDDCs) cultures treated with antibodies in the presence of soluble CD40L. To generate MDDCs, peripheral blood mononuclear cells (PBMCs) from healthy human donors were isolated from leukopacks obtained from the New York Blood Center by Ficoll-Paque density gradient centrifugation. CD14+ cells were purified from PBMCs by positive selection using CD14 human microbeads. Purified CD14+ cells were plated at $3x10^6$ cells per well in a 6-well plate in RPMI 1640 media with 10% FBS, 1x penicillin-streptomycin, 800 U/mL GM-CSF, and 500 U/mL of IL-4. Media was replenished and the complete amount of GM-CSF and IL-4 was added back to cells on day 3 and day 5. On day 6 MDDCs were collected and plated at $1x10^6$ cells per well in a 96-U bottom plate. Anti-CD40xCD40 bispecific antibodies were added to cells simultaneously with a constant dose of CD40L (20 nM). A dose response of CD40L was included as a control. Cells were cultured for 4 days at 37°C, and cell culture supernatant was collected for analysis.

[01606] Cytokine levels in supernatant were analyzed using the MSD V-PLEX cytokine panel 1. MSD V-PLEX assay was performed according to the manufacturer's instruction using cell culture supernatant diluted at 1:2 or 1:20. MSD plates were read using an MESO QuickPlex Sq 120MM instrument and MSD Discovery Workbench software. Data analysis was performed using Graphpad Prism software. The data points obtained were transformed using an X=Log(X) equation, and the transformed data were subjected to a linear regression analysis and fitted into a sigmoidal dose response curve. IC_{50}s were derived from this analysis.

Results

[01607] All four antibodies tested (REGN16334, REGN16335, REGN16431, and REGN16432) blocked IL-12/IL-23p40 production from primary human monocyte derived dendritic cells from two donors in response to stimulation with CD40L (**Figures 4A-4B**). IC_{50} values of antibodies and COMP11209 are shown in **Table 25**.

Table 25: Effect of anti-CD40xCD40 bispecific antibodies on human dendritic cell IL-12/IL-23p40 production in the presence of constant CD40L

Antibody	IC_{50} Donor 1	IC_{50} Donor 2
REGN16334	7.533e-010	5.275e-010
REGN16335	1.576e-010	8.547e-011
REGN16431	1.422e-009	4.972e-010
REGN16432	2.064e-010	9.919e-011
COMP11209	5.938e-010	3.191e-010

Example 8: *In Vitro* Agonist Activity in Human B Cells by Anti-CD40xCD40 Bispecific Antibodies

[01608] To quantify the agonistic activity of anti-CD40xCD40 bispecific antibodies, B cells were incubated with antibodies in the presence of a constant dose of IL-4 (10 pm) without CD40L. Cells were cultured for 3 days at 37°C, and cell culture supernatant was collected for analysis. Cytokine levels in supernatant were analyzed using the MSD V-PLEX proinflammatory panel 1. MSD V-PELX assay was performed according to the manufacturer's instruction using cell culture supernatant diluted 1:2. MSD plates were read using an MESO QuickPlex Sq 120MM instrument and MSD Discovery Workbench software. Data analysis was performed using Graphpad Prism software. The data points obtained were transformed using an X=Log(X) equation, and the transformed data were subjected to a linear regression analysis and fitted into a sigmoidal dose response curve. IC_{50}s were derived from this analysis.

Results

[01609] Analysis of the agonistic activity of antibodies REGN16334, REGN16335, REGN16431, and REGN16432 showed induction of the cytokines IL-6 (**Figures 5A-5B**) and IL-10 (**Figures 6A-6B**) within a range comparable to cells treated with no antibody (IL-4 only) in both donors.

Example 9: Impact of Anti-CD40xCD40 Bispecific Antibodies in a Mouse NP-KLH Immunization Model

[01610] To determine the impact of CD40 blockade on an antigen specific antibody response, a widely used T-dependent immunization model, the NP-KLH immunization model, was utilized in mice homozygous for human CD40 in the place of mouse CD40. Mice were immunized with 25 µg of NP-KLH by subcutaneous injection on the flank with 100 µL of a 1:1 mixture of NP-KLH and alum emulsified by shaking for 30 minutes. For the group receiving alum alone, 100 µL of a 1:1 mixture of PBS and alum was administered. As shown in **Figure 7**, anti-CD40xCD40 bispecific antibody (REGN16334, REGN16335, REGN16431, or REGN16432) or isotype control (REGN4439 or REGN4460) was administered to mice 3 days before immunization, and twice per week following immunization for a total of two weeks at a dose of 1 mg/kg. Following immunization and the antibody treatment protocol, the mice were sacrificed, and blood and inguinal lymph nodes were collected. The blood was collected from all groups of mice by cardiac puncture and transferred into BD microtainer tubes (cat# 365967) for serum isolation.

[01611] For tissue processing, lymph nodes were mashed on a 74-micron cell strainer in 2 mL RPMI media + 10% FBS using the back end of a 3 mL syringe, and single cell suspensions were filtered through Millipore plate filter (100 µm) into a 2 mL deep well plate. Cells were centrifuged at 400g for 4 minutes and resuspended in in 200 µL of PBS. Cells were transferred to a 96 well u-bottom plate, centrifuged at 400g for 4 minutes and stained with a live/dead cell marker for 15 minutes at room temperature. Cells were washed and incubated in Fc block for 15 minutes at 4°C followed by antibody staining with antibody mixes as shown in **Table 26** for 30 minutes at 4°C. After staining, the cells were washed twice with MACS buffer, fixed with BD Cytofix (cat# 554655) diluted 1:4 in PBS for 15 minutes, then resuspended in MACS buffer and stored at 4°C. On the day of acquisition, the cells were washed with BD Perm/wash, incubated in BD Perm/wash buffer (cat# 554723) for 20 minutes and stained with intracellular antibodies (**Table 26**) for 30 minutes. Cells were washed twice and fixed with BD Cytofix, then resuspended in MACS buffer. The cells were then acquired in an FACSymphony A5 instrument and analyzed using OMIQ software. NP+ germinal center B cells were identified as Live → Dump- (dump includes TCRb, CD200R3, Ly6G, CD49b and CD11b) → non-marginal zone B cells (CD1d-) → CD19+B220+ → CD38-IgD- → GC positive (GL7+CD95+)→ NP+. Statistical significance was determined by the Shaprio-Wilk test to assess normality and the Kruskal-Wallis test with Dunn's post-hoc multi-comparison test in GraphPad Prism.

Table 26: Flow Cytometry Panel

	Name&Antigen	Conjugate	Laser	Reactivity	Host	Clone	Isotype	Supplier
Pre-Stain	Live/Dead	Blue	UV 355 nm	N/A	N/A	N/A	N/A	Invitrogen
	Fc Block (CD16/32)	None	N/A	Human	Rat	2.4G2	N/A	TONBO biosciences
	Antigen	Conjugate	Laser	Reactivity	Host	Clone	Isotype	Supplier
Extracellular	CD38	BUV395	UV 355 nm	Mouse/Human	Rat	90/CD38	IgG2a, k	BD
	CD138	BV711	Violet 405 nm	Mouse	Rat	281-2	IgG2a, k	BD
	NP	PE	Yellow-Green 561 nm					Biosearch Tech
	CD95	BV421	Violet 405 nm	Mouse	Hamster	Jo2	IgG2, l	BD
	GL-7	PerCP-Cy5.5	Blue 488 nm	Mouse/Human	Rat	GL7	IgM, k	Biolegend
	IgD	BV786	Violet 405 nm	Mouse	Rat	11-26c.2a	IgG2a, k	BD
	IgA	FITC	Blue 488 nm	Mouse	Rat	C10-3	IgG1, k	BD
	IgG1	BV510	Violet 405 nm	Mouse	Rat	A85-1	IgG1, k	BD
	CD19	BUV737	UV 355 nm	Mouse	Rat	1D3	IgG2a, k	BD
	B220	PE-Cy7	Yellow-Green 561 nm	Mouse	Rat	RA3-6B2	IgG2a, k	BD
	CD98	BV605	Violet 405 nm	Mouse	Hamster	H202-141	IgG2a, k	BD
	CD1d	BUV563	UV 355 nm	Mouse	Rat	WTH2	IgG2a, k	BD
	Dump							
	TCRb	APC	Red 640 nm	Mouse	Hamster	H57-597	IgG, λ1	BD
	CD200R3	APC	Red 640 nm	Mouse	Rat	Ba13		Biolegend
	Ly6G	APC	Red 640 nm	Mouse	Rat	1A8-Ly6g	IgG2a, k	eBioscience
	CD49b	APC	Red 640 nm	Mouse	Rat	DX5	IgM, k	Biolegend
	CD11b	APC	Red 640 nm	Mouse	Rat	M1/70	IgG2b, k	Biolegend
Intracellular	Light Chain k	BV650	Violet 405 nm	Mouse	Rat	187.1	IgG1, k	BD
	Light Chain l	BV650	Violet 405 nm	Mouse	Rat	R26-46	IgG2a, k	BD
	IgA	FITC	Blue 488 nm	Mouse	Rat	C10-3	IgG1, k	BD
	IgG1	BV510	Violet 405 nm	Mouse	Rat	A85-1	IgG1, k	BD
	NP	PE	Yellow-Green 561 nm					Biosearch Tech

Experiment #1 – Methods and Results

[01612] In one experiment, levels of NP-specific IgG1 were qualified in terminal serum by ELISA. NP-2-BSA was diluted in to 4 µg/mL in PBS and 384 well plates were coated with 25 µL/well of solution overnight at 4°C. Plates were washed 4x with wash buffer and blocked with 50 µL/well of 0.5% BSA in PBS for 1 hour at room temperature. Plates were washed 4x with wash buffer and the mouse serum was diluted 1:100 for group A and 1:10,000 for groups B-G. Serum was further serially diluted 3-fold using 0.5% BSA in PBS 8 times and added to plates at 12.5 µL/well. Diluted serum was incubated on plates for 1 hour at room temperature followed by 4x wash. For detection, 25 µL of rat anti-mouse IgG1 HRP conjugated antibody diluted 1:1000 in 0.5% BSA in PBS was added to plates for 1 hour at room temperature. Plates were washed 7x and developed by adding 25 µL of using OptEIA™ TMB Substrate solution. After 20 minutes the reaction was stopped by adding 25 µL 2N sulfuric acid. Absorbance at 450 nm (OD450) was measured on a Molecular Devices SpectraMax M5 plate reader. Relative levels of circulating NP-specific IgG1 in serum were represented as titer units which were defined as dilution factor required to achieve an OD450 reading that was equal to two times background OD450. Graphical analyses were performed using GraphPad Prism software (version 7.0). Statistical significance was determined by the Shaprio-Wilk test to assess normality and the Kruskal-Wallis test with Dunn's post-hoc multi-comparison test in GraphPad Prism.

[01613] In this NP-KLH immunization model, prophylactic treatment with anti-CD40xCD40 bispecific antibody blocked antigen specific germinal center B cell formation in the draining lymph node as quantified by flow cytometry. All of the anti-CD40xCD40 bispecific antibodies reduced the frequency of NP-specific germinal center B cells at 1 mg/kg compared to their relevant isotype controls (**Figure 8A** and **Table 27**). Prophylactic treatment with anti-CD40xCD40 bispecific antibody at 1 mg/kg also blocked the generation of high-affinity NP-IgG1 antibody responses as measured by NP-specific IgG1 titers in serum, with most samples falling below the lower limit of quantification for the assay (**Figure 8B** and **Table 28**).

Table 27: Effect of Anti-CD40xCD40 Bispecific Antibodies on Frequency of NP+ Germinal Center B Cells

Group	Treatment	Antibody Dose	Mean % NP+ Germinal center B cells (Freq. of Live) ± SD	Mean rank difference compared to isotype control
A	Alum (no mAb)	No mAb	0.0006019 ± 0.0002945	N/A
B	REGN4439 (isotype)	1mg/kg	0.2066 ± 0.1413	N/A
C	REGN16334	1mg/kg	0.0005531 ± 0.0005146	21.9 (* p=0.0153)
D	REGN16335	1mg/kg	0.009392 ± 0.01611	14.4 (ns)
E	REGN4460 (isotype)	1mg/kg	0.1693 ± 0.1243	N/A
F	REGN16431	1mg/kg	0.002636 ± 0.00141	10.6 (ns)
G	REGN16432	1mg/kg	0.0005721 ± 0.0004048	20.3 (* p=0.0364)

SD = standard deviation; N/A = not available; ns = not statistically significant. * p<0.05.

Table 28: Effect of Anti-CD40xCD40 Bispecific Antibodies on Frequency of NP IgG1 Titers in Mouse Serum

Group	Treatment	Antibody Dose	Mean NP Titers ± SD	Mean rank difference compared to isotype control
A	Alum (no mAb)	No mAb	*no values detected	N/A
B	REGN4439 (isotype)	1mg/kg	22349 ± 12298	N/A
C	REGN16334	1mg/kg	2942 ± 6576	14.2 (ns)
D	REGN16335	1mg/kg	485.3 ± 925.3	12.1 (ns)
E	REGN4460 (isotype)	1mg/kg	129249 ± 95137	N/A
F	REGN16431	1mg/kg	88.9 ± 126.0	18.1 (* p=0.0412)
G	REGN16432	1mg/kg	*no values detected	22.5 (** p=0.0025)

SD = standard deviation; N/A = not available; ns = not statistically significant. * p<0.05; **p<0.005.

Experiment #2 – Methods and Results

[01614] In another experiment, levels of NP-specific IgG1 were qualified in terminal serum by ELISA. NP-2-BSA was diluted to 4 µg/mL in PBS and 384 well plates were coated with 25 µL/well of solution overnight at 4°C. Plates were washed 5x with wash buffer and blocked with 50 µL/well of 0.5% BSA in PBS for 1 hour at room temperature. Plates were washed 5x with wash buffer and the mouse serum was diluted 1:100 for group A-B and 1:10,000 for groups C-L. Serum was further serially diluted 3-fold using 0.5% BSA in PBS 8 times and added to plates at 12.5 µL/well. Diluted serum was incubated on plates for 1 hour at room temperature followed by 4x wash. For detection, 25 µL of rat anti-mouse IgG1 HRP conjugated antibody diluted 1:1,000 in 0.5% BSA in PBS was added to plates for 1 hour at room temperature. Plates were washed 7x and developed by adding 25 µL of using OptEIA™ TMB Substrate solution. After 20 minutes the reaction was stopped by adding 25 µL 2N sulfuric acid. Absorbance at 450nm (OD450) was measured on a Molecular Devices SpectraMax M5 plate reader. Relative levels of circulating NP-specific IgG1 in serum were represented as titer units which were defined as dilution factor required to achieve an OD450 reading that was equal to two times background OD450. Data analysis was performed using GraphPad Prism. Statistical significance was determined by the Shaprio-Wilk test to assess normality and the Kruskal-Wallis test with Dunn's post-hoc multi-comparison test in GraphPad Prism.

[01615] In this experiment, prophylactic treatment with CD40xCD40 bispecific antibody blocked antigen specific germinal center B cell formation in the draining lymph node as quantified by flow cytometry. All of the tested CD40xCD40 bispecific antibodies reduced the frequency of NP-specific germinal center B cells at 1 mg/kg and higher compared to isotype control (Fig. 9A and **Table 29**). Prophylactic treatment with CD40xCD40 bispecific antibody at 1mg/kg also blocked the generation of high-affinity NP-IgG1 antibody responses as measured by NP-specific IgG1 titers in serum, with most samples falling below the lower limit of quantification for the assay (Fig. 9B and **Table 30**).

Table 29: Effect of CD40xCD40 Bispecific Antibodies on Frequency of NP+ Germinal Center B Cells

Treatment	Antibody Dose	Group	Mean % NP+ Germinal center B cells (Freq. of Live) +/- SD	Mean rank difference compared to isotype control
PBS Only	No mAb	A	0.00007863 ± 0.0001758	N/A
Alum (no mAb)	No mAb	B	0.00168 ± 0.001403	N/A

NP-KLH Only	No mAb	C	0.2042 ± 0.1121	N/A
REGN4439 (Isotype control)	10mg/kg	D	0.2466 ± 0.1856	N/A
REGN16335	0.5mg/kg	E	0.1228 ± 0.2718	11.9 (ns)
	1mg/kg	F	0.0002173 ± 0.0003573	32.9 (ns)
	5mg/kg	G	0.00006046 ± 0.0001352	40.1 (* p=0.0154)
	10mg/kg	H	0.0001546 ± 0.000254	35.8 (ns)
REGN20484	0.5mg/kg	I	0.09259 ± 0.08283	7 (ns)
	1mg/kg	J	0.000671 ± 0.0006068	21.1 (ns)
	5mg/kg	K	0.0002724 ± 0.0003113	31.1 (ns)
	10mg/kg	L	0.00005632 ± 0.00008618	38.2 (* p=0.03)

SD = standard deviation; N/A = not available; ns = not statistically significant. * p<0.05.

Table 30: Effect of CD40xCD40 Bispecific Antibodies on Frequency of NP IgG1 Titers in Mouse Serum

Treatment	Antibody Dose	Group	Mean NP Titers +/- SD	Mean rank difference compared to isotype control
PBS Only	No mAb	A	4.513 ± 7.855	N/A
Alum (no mAb)	No mAb	B	6.582 ± 10.3	N/A
NP-KLH Only	No mAb	C	76584 ± 29915	N/A
REGN4439 (Isotype control)	10mg/kg	D	32900 ± 9061	N/A
REGN16335	0.5mg/kg	E	3762 ± 8409	26 (ns)
	1mg/kg	F	4238 ± 9474	25.6 (ns)
	5mg/kg	G	*no values detected	31.1 (* p=0.0339)
	10mg/kg	H	64.18 ± 141.3	26.2 (ns)
REGN20484	0.5mg/kg	I	10352 ± 14860	19.7 (ns)
	1mg/kg	J	*no values detected	31.1 (* p=0.0339)
	5mg/kg	K	*no values detected	31.1 (* p=0.0339)
	10mg/kg	L	*no values detected	31.1 (* p=0.0339)

SD = standard deviation; N/A = not available; ns = not statistically significant. * p<0.05.

Example 10: Impact of Prophylactic Dosing with Anti-CD40xCD40 Bispecific Antibodies in a Mouse Model of Experimental Autoimmune Encephalomyelitis (EAE)

[01616] To determine the impact of CD40 blockade in an autoimmune disease, a model of experimental autoimmune encephalomyelitis (EAE) model was utilized in mice where the entire mouse CD40 gene was replaced by full-length human CD40 ($CD40^{hu/hu}$ mice). Mice were immunized by subcutaneous injection of 0.1 mL MOG35-55 in emulsion with complete Freund's adjuvant on the upper back and lower back (0.2 mL/mouse total). Two hours following

immunization, mice were administered 150 ng pertussis toxin (PTX) intraperitoneally at 0.1 mL/dose. The administration of PTX was repeated 24 hours later. Anti-CD40 x CD40 bispecific antibodies or isotype controls were administered to mice 3 days before immunization at 25 mg/kg, and twice a week following immunization for a total of five weeks. See, **Figure 10**. Mice were monitored and weighed twice a week for the first two weeks following immunization and daily for weeks 3-5. Mice were assigned a score following the scoring guidelines outlined in **Table 31**. Mice were euthanized after receiving a symptom score of 4 for two consecutive days or upon a score of 4.5 or 5 or when they had dropped 30% of their starting body weight.

Table 31: Mouse EAE Scoring Guidelines

Score	Description
0	**No symptoms**
0.5	**Tip of tail is limp.** When picked up by base of tail, the tail has tension except for the tip. Muscle straining is felt in the tail, while the tail continues to move.
1	**Wholly limp tail.** When picked up by base of tail, instead of being erect, the whole tail drapes over finger. Hind legs are usually spread apart. No signs of tail movement are observed.
1.5	**Limp tail and hind leg inhibition.** When picked up by base of tail, the whole tail drapes over finger. When the mouse is dropped on a wire rack, at least one hind leg falls through consistently. Walking is very slightly wobbly.
2	**Limp tail and weakness of hind legs.** When picked up by base of tail, the legs are not spread apart, but held closer together. When the mouse is observed walking, it has a clearly apparent wobbly walk. One foot may have toes dragging, but the other leg has no apparent inhibitions of movement. - OR - Mouse appears to be at score 0.0, but there are obvious signs of head tilting when the walk is observed. The balance is poor.
2.5	**Limp tail and dragging of hind legs.** Both hind legs have some movement, but both are dragging at the feet (mouse trips on hind feet). - OR - No movement in one leg/completely dragging one leg, but movement in the other leg. - OR - EAE severity appears mild when picked up (as score 0.0-1.5), but there is a strong head tilt that causes the mouse to occasionally fall over.
3	**Limp tail and complete paralysis of hind legs (most common).** - OR - **Limp tail and almost complete paralysis of hind legs.** One or both hind legs are able to paddle, but neither hind leg is able to move forward of the hind hip. - OR - **Limp tail with paralysis of one front and one hind leg.** - OR - **ALL of: Severe head tilting, Walking only along the edges of the cage, Pushing against the cage wall, Spinning when picked up by base of tail.**
3.5	**Limp tail and complete paralysis of hind legs. In addition to: Mouse is moving around the cage, but when placed on its side, is unable to right itself. Hind legs are together on one side of body. - OR - Mouse is moving around the cage, but the hind quarters are flat like a pancake, giving the appearance of a hump in the front quarters of the mouse.**
4	**Limp tail, complete hind leg and partial front leg paralysis.** Mouse is minimally moving around the cage but appears alert and feeding. Mouse will be euthanized if it scores 4.0 for 2 days.

Score	Description
4.5	**Complete hind and partial front leg paralysis, no movement around the cage. Mouse is not alert.** Mouse has minimal movement in the front legs. The mouse barely responds to contact.
	Mice will be euthanized if this score is registered. When the mouse is euthanized because of severe paralysis, a score of 5.0 is entered for that mouse for the rest of the experiment.
5	**Mouse is spontaneously rolling in the cage** - OR - **Mouse is found dead due to paralysis**. - OR - **Mouse is euthanized due to severe paralysis.**

Experiment #1 – Results

[01617] In one experiment using a model of experimental autoimmune encephalomyelitis (EAE), prophylactic blockade of CD40 by anti-CD40xCD40 bispecific antibodies REGN16334, REGN16335, REGN16431, and REGN16432 reduced the severity of EAE disease symptom score relative to no antibody or isotype control treated groups (**Figures 11A-11B** and **Table 32**). In addition to reduction of symptom severity, all CD40 blocking antibodies reduced the percentage of mouse weight loss when compared to no antibody or isotype control treated groups (**Figures 11C-11D** and **Table 33**). The frequency of mice with disease score development was also reduced in groups treated with CD40 blocking antibodies (**Table 34**).

Table 32: Mean EAE Symptom Score

Treatment	Terminal Mean EAE score ± SD	Total Mean EAE score ± SD
Alum (no mAb)	3.71 ± 1.22	2.44 ± 1.83
REGN4439 (Isotype control)	3.21 ± 1.32	2.11 ± 1.65
REGN16334	0.81 ± 1.73	0.71 ± 1.27
REGN16335	0.50 ± 1.07	0.36 ± 0.85
REGN4460 (Isotype control)	2.71 ± 1.07	1.81 ± 1.27
REGN16431	0.83 ± 1.41	0.51 ± 1.10
REGN16432	0.38 ± 1.06	0.26 ± 0.73

Table 33: Mean Weight Loss

Treatment	Terminal % of initial body weight ± SD	Total % of initial body weight ± SD
Alum (no mAb)	69.99 ± 8.18	86.5 ± 12.52
REGN4439 (Isotype control)	76.4 ± 5.72	85.68 ± 10.93
REGN16334	94.8 ± 8.65	94.94 ± 6.56
REGN16335	95.89 ± 9.89	95 ± 7.93

Treatment	Terminal % of initial body weight ± SD	Total % of initial body weight ± SD
REGN4460 (Isotype control)	77.28 ± 6.96	83.06 ± 9.80
REGN16431	95.37 ± 11.89	97.6 ± 7.41
REGN16432	98.21 ± 8.91	95.95 ± 8.35

Table 34: Number of Mice with Development of EAE Symptoms

Antibody (2x weekly)	No. of mice with EAE symptom score
No antibody	7 out of 7
REGN4439 (Isotype control)	7 out of 7
REGN16334	7 out of 8
REGN16335	3 out of 8
REGN4460 (Isotype control)	7 out of 7
REGN16431	4 out of 8
REGN16432	2 out of 8

Experiment #2 – Results

[01618] In another experiment, prophylactic blockade of CD40 by CD40xCD40 bispecific antibodies REGN16335 or REGN20484 reduced the severity of EAE disease symptom score relative to no antibody or isotype control treated groups (Fig. 12A and **Table 35**). In addition to reduction of symptom severity, all CD40 blocking antibodies reduced the percentage of mouse weight loss when compared to no antibody or isotype control treated groups (Fig. 12B and **Table 36**). The frequency of mice with disease score development was also reduced in groups treated with CD40 blocking antibodies (**Table 37**).

Table 35: Mean EAE Symptom Score

Treatment	Terminal Mean EAE score ± SD	Total Mean EAE score ± SD
Alum (no mAb)	2.75 ± 0.98	1.61 ± 1.39
REGN4439 (Isotype control)	1.9 ± 1.26	1.37 ± 1.31
REGN16335	0.6 ± 0.88	0.30 ± 0.64
REGN20484	0.05 ± 0.16	0.03 ± 0.14

Table 36: Mean Weight Loss

Treatment	Terminal % of initial body weight ± SD	Total % of initial body weight ± SD
Alum (no mAb)	69.99 ± 8.18	86.5 ± 12.52
REGN4439 (Isotype control)	76.4 ± 5.72	85.68 ± 10.93
REGN16334	94.8 ± 8.65	94.94 ± 6.56
REGN16335	95.89 ± 9.89	95 ± 7.93
REGN4460 (Isotype control)	77.28 ± 6.96	83.06 ± 9.80
REGN16431	95.37 ± 11.89	97.6 ± 7.41
REGN16432	98.21 ± 8.91	95.95 ± 8.35

Table 37: Number of Mice with Development of EAE Symptoms

Group	Treatment	No. of mice with EAE symptom score
A	Alum (no mAb)	10 out of 10
B	REGN4439 (Isotype control)	10 out of 10
C	REGN16335	5 out of 10
D	REGN20484	3 out of 10

Example 11: CD40L blockade reduces the antibody response to AAV, but enables only partial transduction upon vector re-administration

[01619] To test the impact of CD40L blockade to enable vector re-administration, a study was conducted in mice, outlined in **Figure 13**. C57BL/6 mice (n=4-5 mice per group) were dosed prophylactically two times with 500 µg of anti-mouse CD40L blocking antibody (InVivoMAb anti-mouse CD40L (CD154), clone MR-1, bioxcell.com/invivomab-anti-mouse-cd40l-cd154-be0017-1, BioXcell, Lebanon, NH), subcutaneously under the skin on the back. Control mice were left untreated. Anti-CD40L antibody-injected and control mice were then dosed with a recombinant AAV8 vector ("AAV #1," encoding human lysosomal acid alpha glucosidase with an N-terminal fusion to a human single-chain variable fragment specific to human CD63; hereafter, "anti-CD63 scFv:hGAA") intravenously via retroorbital injection at 6.56e11 vector genomes per kilogram body weight (vg/kg). After AAV #1 injection, the treatment group continued to receive subcutaneous administration of 500 µg of anti-CD40L antibody every three days, until day 28 of the study. Mice were bled at defined intervals for serum anti-AAV antibody analyses.

[01620] To assess whether CD40L-mediated blockade impacted the development of antibody responses to AAV, serum levels of anti-AAV capsid IgG were quantified at defined timepoints by

ELISA. Specifically, 96-well flat-bottom plates were coated with 1e9 vg/well recombinant AAV8 vector in DPBS overnight. The next day, plates were washed and blocked prior to addition of serum samples at serial 3x dilutions, beginning at an initial dilution of 1:300. Serum was incubated overnight at 4°C. The next day, plates were repeatedly washed prior to incubation with an anti-mouse-IgG Fcg Fragment-HRP-conjugated polyclonal secondary antibody (Jackson Immunoresearch, West Grove, PA). Plates were again repeatedly washed prior to development with TMB Substrate solution. After 20 minutes, the reaction was stopped by addition of 2N phosphoric acid. Absorbance at 450 nm (OD450) was measured on a SpectraMax i3 plate reader (Molecular Devices, San Jose, CA). Relative levels of serum anti-AAV8 IgG were determined and plotted as titer values using Prism v.9 software (GraphPad, Boston, MA). Titer was defined as the dilution factor required to achieve an OD450 reading equal to 2-fold higher than background values.

[01621] As shown in **Figure 14**, antibody-mediated CD40L blockade led to suppression of anti-AAV IgG antibody responses compared to mice that were not treated with antibody, which mounted strong antibody titers.

[01622] To test whether reduced antibody titers observed in anti-CD40L-treated mice could enable AAV vector re-administration, mice were dosed with a second AAV vector ("AAV #2") encoding eGFP, 84 days after receiving AAV #1 (see, e.g., **Figure 13**). Mice were sacrificed 4 days later for analysis of eGFP transgene DNA and RNA in the liver by quantitative polymerase chain reaction (qPCR). As shown in **Figures 15A-15B**, mice that received anti-CD40L antibody blockade exhibited detectable levels of eGFP transgene DNA and mRNA versus mice that were not treated with antibody. However, these DNA and mRNA levels were on average lower than that of mice that were previously naïve to AAV. To further assess eGFP transduction in liver, immunohistochemical analysis of eGFP protein expression was performed on formalin-fixed liver tissue sections, and eGFP+ area was quantified using HALO software (Indica Labs). Consistent with eGFP transgene DNA and mRNA, eGFP protein expression was significantly higher in anti-CD40L antibody treated mice versus mice that received no antibody treatment (**Figure 15C**). However, also consistent with eGFP transgene DNA and mRNA findings, the level of eGFP protein expression was again on average lower than that of mice that were previously naïve to AAV.

[01623] Collectively, these data show that while antibody-mediated blockade of CD40L can suppress antibody responses to AAV vectors, targeting CD40L alone was not sufficient to enable vector re-transduction at levels equivalent to that observed in animals receiving the vector for the first time. These findings are supported by findings in previous reports, which

found that CD40L blockade enabled only partial transduction upon vector re-administration, and that treatment with additional immunomodulatory agents was needed to achieve higher levels of transduction (Manning et al 1998).

Example 12: Impact of prophylactic short-term CD40 blockade using anti-CD40 antibodies on development of anti-AAV antibody responses

[01624] CD40 is constitutively expressed by both B cells and professional antigen presenting cells, whereas expression of its ligand (CD40L) is induced on T cells following activation. Because of this, the inventors reasoned that CD40 blockade may be more effective than CD40L blockade at suppressing anti-AAV antibody responses, since complete CD40 receptor occupancy (and thus more complete blockade of CD40-CD40L interactions that facilitate B cell activation) could be achieved prior to immune activation, rather than concurrent with immune activation. To test this, a study using anti-CD40xCD40 bispecific antibodies in CD40-humanized mice was conducted as outlined in **Figure 16**. CD40-humanized mice are mice in which the entire mouse CD40 gene has been replaced with the gene encoding the full-length human CD40 protein; homozygous CD40-humanized mice ($CD40^{hu/hu}$) are therefore functionally knocked-out for mouse CD40, and instead possess two copies of the human CD40 gene. These mice mount antibody responses at levels similar to wild-type CD40 mice as described herein. As shown in **Figure 16**, mice (n=4-5 mice per group) were first administered two prophylactic doses of anti-CD40xCD40 bispecific antagonist antibody (REGN16335 or REGN16334) or equivalent human IgG4 with Fc mutation isotype control (REGN4439), subcutaneously under the neck or back skin at 25 milligrams per kilogram body weight (25 mg/kg). In the same manner, separate groups of mice received a conventional anti-CD40 antagonist monoclonal human IgG1 with Fc mutation (COMP11209) or human IgG1 isotype control (H1H10126P) at 25 mg/kg. Mice were then administered an AAV8 vector ("AAV #1," encoding human lysosomal acid alpha glucosidase with an N-terminal fusion to a human single-chain variable fragment specific to human CD63; hereafter, "anti-CD63 scFv:hGAA") intravenously via retroorbital injection at 6.56e11 vg/kg. Mice continued to receive injections of anti-CD40 bispecific or monoclonal antibody, or isotype controls, twice per week for four weeks, and were bled at defined intervals for serum anti-AAV antibody analyses, as described in Example 11. For anti-IgM AAV antibody analysis, an anti-mouse-IgM μ-chain-specific polyclonal HRP-conjugated antibody was used in place of the anti-IgG HRP-conjugated secondary antibody.

[01625] As shown in **Figure 17A**, *in vivo* CD40 blockade with anti-CD40xCD40 bispecific antibodies (REGN16335 or REGN16334) or anti-CD40 mAb (COMP11209) resulted in marked suppression of anti-AAV8 IgG antibody titers to levels similar to AAV-naïve animals that did not receive AAV #1 ("AAV #2 only"). By contrast, isotype control-treated mice, or mice treated with no antibody, showed robust and persistent AAV IgG responses. Evaluation of anti-AAV8 IgM titers also revealed a partial inhibitory effect of anti-CD40 antibodies (**Figure 17B**). Thus, these data demonstrate that CD40 blockade with anti-CD40 antibodies can potently suppress *de novo* IgG responses following AAV vector administration.

Example 13: Impact of prophylactic CD40 blockade on ability to systemically re-administer AAV vector

[01626] To determine whether the lower anti-AAV antibody titers observed in anti-CD40 antibody-treated mice were sufficient to enable AAV8 vector re-administration, mice were treated ~3 months later with a second AAV8 vector ("AAV #2," AAV8 CAG eGFP) via intravenous retroorbital injection at a dose of 6.56e12 vg/kg. Ten days after treatment, mice were sacrificed, and eGFP transgene DNA and mRNA levels were evaluated in liver by quantitative real-time PCR (qPCR). As shown in **Figures 18A-18B**, mice treated with anti-CD40xCD40 bispecific Abs or anti-CD40 mAb showed detectable GFP transgene DNA and mRNA at levels comparable to transduction control mice receiving only AAV #2 (previously AAV-naïve). To evaluate eGFP protein expression, eGFP immunohistochemical (IHC) analysis was performed on formalin-fixed, paraffin-embedded liver tissue, and eGFP+ area was quantified using HALO software (Indica Labs). IHC analysis showed that eGFP protein expression was significantly higher in anti-CD40xCD40 antibody and anti-CD40 mAb-treated mice versus mice that received the corresponding isotype controls, and comparable to levels in mice that received the eGFP vector only (**Figure 18C**). These data show that antibody-mediated CD40 blockade can enable systemic AAV re-transduction at levels equivalent to previously AAV-naïve animals.

Example 14: Impact of prophylactic CD40 blockade on formation of germinal center B cell responses

[01627] Productive antibody responses to T cell-dependent antigens, including formation of long-lived B cell immunological memory and plasma cells, depend on repeated CD40-CD40L interactions between a subset of activated B cells, known as germinal center (GC) B cells, and

specialized CD4+ helper T cells known as follicular T helper cells (TFH). In this Example, whether antibody-mediated CD40 blockade can mechanistically ablate AAV-induced GC B cell responses was evaluated. Specifically, a study was conducted in $CD40^{hu/hu}$ mice in which mice were treated with AAV8 vector intravenously (6.56e11vg/kg, i.v.) in the presence of anti-CD40xCD40 antibody, anti-CD40 mAb, or respective isotype control (outlined in **Figure 19**; n=6 mice per group). Eleven days after treatment with AAV, mice were sacrificed for flow cytometry analysis of total and AAV-specific GC B cells in spleen. Specifically, single-cell splenocyte suspensions were prepared by mechanical disruption. Cells were transferred to a 96-well U-bottom plate, centrifuged at 400 x g for 4 minutes and stained with a fixable viability dye for 15 minutes at room temperature. Cells were washed and incubated in Fc block for 15 minutes at 4°C. For detection of AAV-specific B cells, splenocytes were incubated with AAV8 for 1 hour on ice, (MOI 10,000) to facilitate interactions between AAV particle and antigen-specific B cell receptors (BCRs), followed by detection with anti-AAV8 biotinylated antibody (Progen) and Streptavidin-PE conjugate. Additional antibody staining was conducted with one of two antibody mixes as shown in **Table 38** for 30 minutes at 4°C. After staining, the cells were washed twice with a BSA- and EDTA-containing wash buffer, fixed with BD Cytofix (cat# 554655) diluted 1:4 in PBS for 15 minutes, then resuspended in wash buffer and stored at 4°C. The cells were then acquired on a FACSymphony A5 instrument and analyzed using OMIQ software. GC B cells were gated as follows: Live cells → Dump- (TCRb, CD200R3, Ly6G, CD49b and CD11b) → non-marginal zone B cells (CD1d-) → CD19+B220+ → CD38-IgD- → GC positive (GL7+CD95+)→ AAV+/-

[01628] Analysis of total and AAV-specific GC B cells revealed that mice treated with anti-CD40xCD40 bispecific antibody or anti-CD40 mAb showed substantially reduced total GC and AAV-specific GC B cells relative to mice treated with relevant isotype controls or no antibody (**Figures 20A-20D**). Therefore, antibody-mediated CD40 blockade can prevent the formation of AAV-specific GCs, and suppress existing GC reactions.

Table 38: Description of Antibodies Used for Cell Staining

Pre-Stain						
Name/Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
Live/Dead	Blue	N/A	N/A	N/A	N/A	Invitrogen
Fc Block (CD16/32)	None	Human	Rat	2.4G2	N/A	TONGO biosciences
Surface stain						
Name/Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
B220	BUV395	Mouse	Rat	RA3-6B2	IgG2a, κ	BD
CD3	BUV805	Mouse	Rat	17A2	IgG2b, κ	BD
CD40L	BUV737	Mouse	Armenian Hamster	MR1	IgG3, κ	BD
OX40	BV786	Mouse	Rat	OX-86	AO IgG1, κ	BD
CD25	BV510	Mouse	Rat	PC61	IgG1, λ	Biolegend
PD-1	PE-Cy7	Mouse	Rat	RMP1-30	IgG2b, κ	Biolegend
CD44	APC-Cy7	Mouse	Rat	IM7	IgG2b, κ	Biolegend
ICOS	APC	Mouse	Syrian Hamster	15F9	IgG	Biolegend
CD4	BUV496	Mouse	Rat	GK1.5	IgG2b, κ	BD
CXCR5	BV605	Mouse	Rat	L138D7	IgG2b, κ	Biolegend
CD8	Alexa Fluor 488	Mouse	Rat	53-6.7	IgG2a, κ	BD
CD19	BV711	Mouse	Rat anti-Mouse	1D3	IgG2a κ	BD
Intracellular stain						
Name/Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
FOXP3	PerCP Cy5.5	Mouse	Rat	FJK-16s	IgG2a κ	eBioscience
Ki-67	PE	Human / Mouse	Mouse	B56	IgG1, κ	BD

Example 15: Impact of prophylactic CD40 blockade using anti-CD40 antibodies on generation of anti-AAV T cell responses

[01629] In addition to its roles in regulating B cell immune responses, CD40-CD40L interactions are also known to participate in T cell immune responses via licensing of professional antigen presenting cells, which constitutively express CD40. In the context of AAV, mice deficient for CD40L, or mice administered CD40L blocking antibodies, show reduced T cell responses to AAV (Mays et al 2009, Shirley et al 2020). In this Example, the impact of antibody-mediated blockade of CD40 receptor on the T cell response immune response to AAV is evaluated. Specifically, $CD40^{hu/hu}$ mice were treated prophylactically with anti-CD40xCD40-bispecifc antibody, anti-CD40 mAb, or corresponding isotype control. Mice were subsequently treated with an AAV8 vector (as outlined in Example 14 and **Figure 19**) and systemic T cell responses were evaluated in spleen by flow cytometry and IFNg ELISpot assay 11 days later. Flow cytometry analysis was conducted essentially as in Example 14, except that cells were stained with the antibodies indicated in **Table 39**. Additionally, for analysis of proliferating T cells, on the day of acquisition, the cells were washed with BD Perm/wash, incubated in BD Perm/wash buffer (cat# 554723) for 20 minutes and stained with antibody against the proliferation marker

Ki-67, for 30 minutes. Cells were subsequently washed twice and fixed with BD Cytofix. The cells were then acquired on a FACSymphony A5 instrument and analyzed using OMIQ software. TFH cells were gated as follows: Live → CD19- B220- → CD8- CD4+ → CD44+ → PD-1hi CXCR5hi. Proliferating CD4+ T cells were gated as follows: Live → CD19- B220- → CD8- CD4+ → Ki-67+. IFNg ELISpot analysis was carried out essentially as described in the manufacturer's protocol (Mabtech), except that 5e5 splenocytes were plated per well in duplicate, and cells were stimulated with a peptide pool containing overlapping 15-mer peptides spanning the entire VP1 sequence of AAV8 (Pepmix AAV8 JPT Peptide Technologies GmbH, Berlin, Germany), 5 µg/peptide.

Table 39: Description of Antibodies Used for Cell Staining

Pre-Stain						
Name/Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
Live/Dead	Blue	N/A	N/A	N/A	N/A	Invitrogen
Fc Block (CD16/32)	None	Human	Rat	2.4G2	N/A	TONGO biosciences

Surface stain						
Name/Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
B220	BUV395	Mouse	Rat	RA3-6B2	IgG2a, κ	BD
CD3	BUV805	Mouse	Rat	17A2	IgG2b, κ	BD
CD40L	BUV737	Mouse	Armenian Hamster	MR1	IgG3, κ	BD
OX40	BV786	Mouse	Rat	OX-86	AO IgG1, κ	BD
CD25	BV510	Mouse	Rat	PC61	IgG1, λ	Biolegend
PD-1	PE-Cy7	Mouse	Rat	RMP1-30	IgG2b, κ	Biolegend
CD44	APC-Cy7	Mouse	Rat	IM7	IgG2b, κ	Biolegend
ICOS	APC	Mouse	Syrian Hamster	15F9	IgG	Biolegend
CD4	BUV496	Mouse	Rat	GK1.5	IgG2b, κ	BD
CXCR5	BV605	Mouse	Rat	L138D7	IgG2b, κ	Biolegend
CD8	Alexa Fluor 488	Mouse	Rat	53-6.7	IgG2a, κ	BD
CD19	BV711	Mouse	Rat anti-Mouse	1D3	IgG2a κ	BD

Intracellular stain						
Name/Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
FOXP3	PerCP Cy 5.5	Mouse	Rat	FJK-16s	IgG2a κ	eBioscience
Ki-67	PE	Human / Mouse	Mouse	B56	IgG1, κ	BD

[01630] Flow cytometry analysis of splenic T cells from mice treated with anti-CD40xCD40 bispecific antibody or anti-CD40 mAb revealed strong suppression of total numbers and frequencies of follicular helper T cells (TFH), essential regulators of B cell germinal center responses (**Figures 21A-21B**), relative to mice treated with isotype controls or no antibody. Moreover, a more general reduction in number and frequency of proliferating CD4+ T cells (Ki-67+; **Figures 21C-21D**) was also observed.

[01631] Analysis of antigen-specific T cell responses by IFNg ELISpot revealed suppression of anti-capsid T cell responses in anti-CD40xCD40 bispecific antibody and anti-CD40 mAb-treated animals versus isotype control mice or mice that were not treated with antibody (**Figure 21E**). Thus, prophylactic antibody-mediated CD40 blockade can also be effectively utilized to suppress T cell responses to AAV, and may therefore represent an effective strategy to prevent elimination of transduced cells, or related pathology, resulting from T cell immune responses to transgene or capsid.

Example 16: Impact of prophylactic CD40 blockade using anti-CD40 antibodies on development of anti-transgene antibody responses

[01632] Antibody responses to transgene products may develop following AAV gene therapy, and reduce therapeutic efficacy by impacting transgene product biodistribution or activity. To assess whether antibody-mediated CD40 blockade also prevents development of anti-transgene antibody responses, mice were treated with an AAV8 vector encoding a human lysosomal enzyme fused to an scFv antibody fragment, in the presence or absence of anti-CD40xCD40 bispecific antibodies, anti-CD40 mAb, or corresponding isotype control antibodies, as described in Example 12 and **Figure 13**. Anti-transgene antibody titers were then monitored in serum samples collected in the weeks following AAV treatment, essentially as described in Example 12, except that the ELISA plates were coated with the relevant recombinant human human lysosomal enzyme scFv fusion protein.

[01633] While mice treated with either no antibody or isotype control developed mild to moderate IgG and/or IgM responses against the human lysosomal enzyme scFv fusion transgene protein, anti-GAA IgG and/or IgM responses were fully suppressed in mice that received anti-CD40xCD40 bispecific or anti-CD40 mAb blocking antibodies (**Figure 22**). Thus, these data suggest that antibody-mediated CD40 blockade may also be utilized to prevent undesired antibody responses to transgene product.

[01634] Examples herein provide support for use of anti-CD40 receptor blocking antibodies to enable administration of a second AAV vector ("vector re-administration"). While there is some evidence to suggest that partial transduction with a second AAV vector may be achieved with antibody blockade of the ligand (CD40L), that the use of CD40L deficient mice may improve vector re-administration, and that anti-CD40L antibodies may suppress antibody responses to other vectors, in each instance, CD40L deficiency / blockade either failed to adequately suppress antibody responses to the vector, or failed to achieve transgene levels on second

vector administration that were comparable to that of naïve animals receiving AAV for the first time. By contrast, the data with anti-CD40xCD40 bispecific and anti-CD40 mAb blocking antibodies described herein shows that antibody responses to AAV capsid are strongly attenuated and that transgene expression is achieved at levels similar to that of naïve animals on vector re-administration. Antibody responses to the transgene are also completely attenuated.

[01635] Examples herein further provide support for use of anti-CD40 receptor blocking antibodies to attenuate T cell immune responses to AAV.

[01636] Based on studies described herein, without wishing to be bound by theory, the mechanism of action of T cell inhibition can be through inhibition of antigen presenting cell (APC) licensing, including licensing of dendritic cells, macrophages, and B cells.

Example 17: CryoEM Analysis of anti-CD40xCD40 Bispecific Antibodies

[01637] To better understand the binding of REGN16335 and REGN16334 to CD40, structural analysis was performed via cryo-electron microscopy (cryo-EM). Fab fragments were prepared enzymatically. The Fab fragment 30027P2 corresponds to arm 1 of REGN16335, the Fab fragment 21519P2 corresponds to arm 1 of REGN16634, and the Fab fragment 21520P2 corresponds to arm 2 for both REGN16335 and REGN16334.

[01638] A 3D reconstructed map of the complex of CD40 with the three Fab arms (30027P2, 21519P2, and 21520P2) with resolution of 3 Å shows that the three arms bind non-overlapping epitopes spanning the CRD1, CRD2, and CRD3 domains (**Figure 23**). The 30027P2 Fab mostly binds the CRD1 domain and a small portion of CRD2, the 21520P2 Fab binds across CRD1 and CDR2 domains, and the 21519P2 Fab binds across CRD2 and CRD3 domains.

Example 18. Combination of Anti-BCMAxCD3 to Eliminate Pre-Existing Immunity to AAV and CD40 Blockade to Prevent New Antibody Response to AAV on Subsequent AAV Exposure

[01639] In this Example, anti-BCMAxCD3 is used to eliminate pre-existing immunity to AAV, while anti-CD40 antibody (e.g., REGN16335, iscalimab, ravagalimab, BI-655064, or abiprubart) or other CD40 inhibitor (e.g., CD40L binding protein such as tegoprubart of dazodalibep) is utilized to prevent any new antibody response to AAV on subsequent AAV exposure. Specifically, in individuals with pre-existing antibody responses to AAV, anti-BCMAxCD3, given either alone or in combination with FcRn blockade (or similar IgG depletion strategy) and/or B cell depletion, is initiated to reduce an anti-AAV antibody response. Once anti-AAV antibodies

reach sub-neutralizing levels, anti-CD40 antibody (e.g., REGN16335, iscalimab, ravagalimab, BI-655064, or abiprubart) or other CD40 inhibitor (e.g., CD40L binding protein such as tegoprubart of dazodalibep) treatment is started, and a therapeutic AAV is dosed in the days or weeks thereafter. A new antibody response against AAV is thereby prevented. Thus, anti-BCMAxCD3 returns an individual with pre-existing antibody immunity to an effectively immunologically naïve status, while CD40 blockade preserves naïve status upon therapeutic AAV exposure, therefore allowing for AAV re-dosing in the future.

Example 19. Combination of Anti-BCMAxCD3 to Eliminate Potential Residual Antibody Responses Following AAV Exposure in Presence of CD40 Blockade

[01640] In this Example, anti-BCMAxCD3 is used to eliminate potential residual antibody responses generated following AAV exposure in the presence of CD40 blockade, thereby rescuing the ability to re-dose AAV. Specifically, CD40 blockade (e.g., with anti-CD40 antibody (e.g., REGN16335, iscalimab, ravagalimab, BI-655064, or abiprubart) or other CD40 inhibitor (e.g., CD40L binding protein such as tegoprubart of dazodalibep)) is initiated prior to AAV treatment. After AAV exposure, reduced but measurable antibody titers are generated to the AAV capsid. Treatment with anti-BCMAxCD3, either alone or in combination with FcRn blockade (or similar IgG depletion strategy) and/or B cell depletion, is then initiated to bring residual antibody titers to sub-neutralizing levels. A second AAV therapeutic (either the same or different) is then administered, and transduction is successful. Thus, in scenarios where CD40 blockade attenuates but does not fully eliminate antibody titers to AAV, anti-BCMAxCD3 can be used to reduce titers to levels that enable AAV re-dosing.

Example 20. Combination of CD40 Blockade Administered Concomitantly with Anti-BCMAxCD3 to Block Ongoing Antibody Responses to AAV from Recent Exposure

[01641] In this Example, CD40 blockade (e.g., with anti-CD40 antibody (e.g., REGN16335, iscalimab, ravagalimab, BI-655064, or abiprubart) or other CD40 inhibitor (e.g., CD40L binding protein such as tegoprubart of dazodalibep)) is administered concomitantly with anti-BCMAxCD3 to block ongoing antibody responses to AAV from recent exposure. Specifically, in individuals with pre-existing antibody responses to AAV, anti-BCMAxCD3 is administered with anti-CD40 antibody in a single or repeated dose regimen. FcRn blockers (or similar IgG depletion strategy) may also be used. Whereas anti-BCMAxCD3 depletes antibody-secreting cell populations, CD40 blockade prevents new B cell activation and terminates ongoing B cell

responses that would otherwise not be impacted by anti-BCMAxCD3 treatment alone. Thus, CD40 blockade enhances the therapeutic effect of anti-BCMAxCD3.

Example 21. Plasma cell depletion in combination with neonatal Fc receptor (FcRn) blockade elicits rapid and deep suppression of pre-existing anti-AAV antibody titers

[01642] For adeno-associated virus gene therapy, the generation of neutralizing antibodies after exposure precludes the ability to re-administer AAV vectors of the same or related serotypes, despite therapeutic need. Furthermore, due to natural exposure to wild-type AAVs, roughly 30-60% of individuals harbor pre-existing antibodies to AAV that prevent administration of even a single AAV vector. Therefore, strategies that can attenuate pre-existing anti-AAV antibody responses induced by either recombinant or wild type AAVs have the potential to greatly expand the versatility and accessibility of AAV gene therapies to a broader patient population. In some embodiments, the subsequently administered AAV vector has a capsid derived from the same AAV serotype as the originally administered AAV vector.

[01643] Because plasma cells are the source of long-lived antibody responses, it was reasoned that antibody-mediated plasma cell depletion may suppress pre-existing antibody responses to AAV sufficiently to enable AAV vector transduction or re-transduction in seropositive animals. To test this, B cell maturation antigen (BCMA)- and CD3 gamma-, CD3 delta-, and CD3 epsilon-humanized mice (n=6 per group) were treated with 1e12 vector genomes (vg) per kilogram (kg) recombinant AAV8 (encoding a promoterless transgene) to induce a strong anti-capsid antibody response (e.g., high-titer nAbs). 73 days later, a timepoint deemed sufficient to account for long-lived plasma cell differentiation, mice were injected subcutaneously weekly for five weeks with 25 milligrams (mg) per kg with linvoseltamab, also known as REGN5458, a fully-human T cell-bridging bispecific antibody targeting B cell maturation antigen and CD3 (referred to herein as “anti-BCMAxCD3 bispecific antibody”) to induce plasma cell depletion. Additionally, because the half-life of immunoglobulin G is relatively long (~6-8 days in mice and ~21 days in humans) due to the action of neonatal Fc receptor (“FcRn”), it was also evaluated whether additional blockade of FcRn with efgartigimod alfa, administered subcutaneously weekly at 20 mg/kg, could further accelerate and improve titer reductions elicited by plasma cell depletion. Finally, to capture a wider range of AAV-specific B cells that may not express high levels of BCMA, such as committed memory B cells and early plasmablasts, it was also tested whether additional B cell depletion with a cocktail of anti-CD19/CD20 antibodies, administered subcutaneously weekly at 25mg/kg each, may further improve the therapeutic effect of plasma cell depletion with anti-BCMAxCD3 bispecific antibody. Mice were bled at defined intervals for serum anti-AAV

antibody analysis. A schematic of the full experimental design is presented in **Figure 24**. To prevent any initial impact of efgartigimod alfa on the therapeutic effect of anti-BCMAxCD3 bispecific antibody or anti-CD19/CD20 antibodies, which are themselves immunoglobulins, efgartigimod alfa was omitted from the first week's treatment cocktails.

[01644] To evaluate the impact of plasma cell depletion, FcRn blockade, B cell depletion, or combinations thereof on anti-AAV8 IgG titers, anti-capsid IgG levels were measured in serum of mice over time. Specifically, 96 well flat-bottom plates were coated with 1e9 vg/well recombinant AAV8 vector in DPBS overnight. The next day, plates were washed and blocked with 0.5% bovine serum albumin in DPBS for 1hr. Serum samples were then diluted 3x, beginning at an initial dilution of 1:300 and ending at a dilution of 53,144,100. Diluted serum was then transferred to the assay plate and incubated overnight at 4°C. The next day, the assay plates were repeatedly washed prior to incubation with an anti-mouse-IgG Fc-gamma Fragment-HRP-conjugated polyclonal secondary antibody (Jackson Immunoresearch, West Grove, PA). Plates were again repeatedly washed prior to development with TMB substrate solution. After 20 minutes, the reaction was stopped by addition of 2N phosphoric acid. Absorbance at 450 nm (OD450) was measured on a SpectraMax i3 plate reader (Molecular Devices, San Jose, CA). Relative levels of serum anti-AAV8 IgG were determined and plotted as titer values using Prism v.9 software (GraphPad, Boston, MA). Titer was defined as the dilution factor required to achieve an OD450 reading equal to 2-fold higher than background values.

[01645] It was found that while anti-AAV8 antibody titers showed minor declines over time in mice administered either anti-BCMAxCD3 bispecific antibody, efgartigimod alfa, or anti-CD19/CD20 antibodies individually, the titer reductions were minor and not statistically different from AAV-treated mice that received no immunomodulation. By contrast, mice receiving a cocktail of anti-BCMAxCD3 bispecific antibody and efgartigimod alfa showed rapid titer declines to naïve or near-naive levels, and mice additionally treated with anti-CD19/CD20 antibodies showed even more rapid and complete titer declines, with all 6/6 mice exhibiting titers below the limit of detection by the cessation of the five-week treatment period (**Figure 25**). Thus, these data demonstrate that anti-AAV8 titers can be suppressed by therapeutic plasma cell depletion, with the timeframe required for anti-AAV8 titer depletion reduced by FcRn blockade. Additionally, the depth of titer reduction can be further enhanced with B cell depletion in mice.

Example 22. Plasma cell depletion in combination with FcRn blockade enables AAV vector re-administration

[01646] Next was evaluated whether the deep titer reductions observed in mice following combination treatment of anti-BCMAxCD3 bispecific antibody and efgartigimod alfa, and following combination treatment of anti-BCMAxCD3 bispecific antibody, efgartigimod alfa, and anti-CD19/CD20 antibodies, could enable re-transduction with a second AAV vector. To this end, the mice from Example 21 were treated intravenously with 3e12 vg/kg AAV8 GFP, then sacrificed 10 days later to evaluate transgene expression in liver (**Figure 24**). While nearly all mice receiving no immunomodulation or single-agent immunomodulation failed to achieve any re-transduction in liver, due to presence of anti-AAV8 antibodies from previous AAV8 exposure, significant levels of GFP transgene DNA (**Figure 26**) and RNA (**Figure 27**) were observed in mice receiving anti-BCMAxCD3 bispecific antibody + FcRn blocker, and less frequently in mice receiving anti-BCMAxCD3 bispecific antibody + anti-CD19/CD20 antibodies, as measured by quantitative real-time PCR and quantitative real-time reverse transcription PCR, respectively. 3/6 mice receiving anti-BCMAxCD3 bispecific antibody + FcRn blocker achieved re-transduction equivalent to seronegative control mice. The greatest level of re-transduction was observed in the triple combination group, with 6/6 mice achieving transgene levels equivalent to that of previously naive mice. Immunohistochemical staining of formalin-fixed, paraffin-embedded liver sections for GFP transgene protein corroborated these findings (**Figures 28A-28B**). Together, these data indicate that anti-BCMAxCD3 bispecific antibody-mediated plasma cell depletion, particularly in combination with FcRn blockade, can enable AAV re-dosing, or other immunogenic gene therapy vectors, regardless of serostatus, and that the success rate for re-dosing may be further enhanced by B cell depletion in mice.

Example 23. Analysis of plasma cell frequencies and counts in spleen and bone marrow following anti-BCMAxCD3 bispecific antibody treatment

[01647] To confirm on-target activity of anti-BCMAxCD3 bispecific antibody, plasma cell numbers in bone marrow and spleen were evaluated by flow cytometry at the time of sacrifice (**Figure 24**). Specifically, single-cell splenocyte suspensions were prepared by mechanical disruption of spleen. For bone marrow extraction, femurs were cut at both ends, placed in a PCR plate with holes punched at the bottom, and spun down for 3 minutes at 500g. Red blood cells were lysed using ACK lysis buffer. Cells were transferred to a 96 well U-bottom plate, centrifuged at 400g for 4 minutes and stained with LIVE/DEAD Fixable Blue Dead Cell dye (ThermoFisher) for 15 minutes at room temperature. Cells were washed and incubated in Fc

block (Tonbo Biosciences) for 15 to 30 minutes at 4°C. For detection of AAV-specific B cells, splenocytes were incubated with recombinant AAV8 for 1hr on ice, (multiplicity of infection [MOI] of 10,000) to facilitate interactions between AAV particles and antigen-specific BCRs, followed by washing and labeling with anti-AAV8 biotinylated antibody (clone ADK8, Progen) and surface stain antibody cocktail (**Table 40**) for 30 minutes at 4°C in Brilliant Stain buffer (BD Biosciences). Cells were again washed and then stained with Streptavidin-PE conjugate (Biolegend) for an additional 20 minutes at 4°C, followed by washing and fixation with BD Cytofix (BD Biosciences). For intracellular staining, samples were washed and incubated in 1x Perm/Wash buffer (BD Biosciences) for 20 minutes and resuspended in intracellular stain (**Table 40**) for 30 minutes at 4°C followed by washing and fixation with BD Cytofix (BD Biosciences). CountBright Absolute counting Beads (ThermoFisher) were used according to the manufacturer's protocol to enumerate absolute cell counts. Acquisition was performed on a BD FACSymphony A5 using FACSDiva software. Analysis was performed using FlowJo or OMIQ software. All B cells were first gated according to light scatter properties, then negatively gated to exclude viability dye positive and non-B cell lineage marker positive cells. Specific B cell populations were then gated as follows: Naïve B cells, CD19+ B220+ CD1d- IgD+ CD38+; Memory B cells, CD19+ B220+ CD1d- IgD- CD38+ AAV+/-; Plasma cells: B220- IgD- CD138+ Light Chain+.

Table 40. The flow cytometry antibody staining panel used in **Figures 29A-29J**.

Pre-Stain						
Reagent / Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
Live/Dead	Blue	N/A	N/A	N/A	N/A	Invitrogen
AAV8	None	N/A	N/A	N/A	N/A	N/A
Fc Block (CD16/32)	None	Human	Rat	2.4G2	N/A	TONGO biosciences
Surface stain						
Antigen	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
CD38	BUV395	Mouse/Human	Rat	90/CD38	IgG2a, k	BD
CD138	BV711	Mouse	Rat	281-2	IgG2a, κ	BD
CD95	BV421	Mouse	Hamster	Jo2	IgG2, λ	BD
GL-7	PerCP-Cy5.5	Mouse/Human	Rat	GL7	IgM, k	Biolegend
IgD	BV786	Mouse	Rat	11-26c.2a	IgG2a, k	BD
IgA	FITC	Mouse	Rat	C10-3	IgG1, κ	BD
IgG1	BV510	Mouse	Rat	A85-1	IgG1, κ	BD
CD19	BUV737	Mouse	Rat	1D3	IgG2a, κ	BD
B220	PE-Cy7	Mouse	Rat	RA3-6B2	IgG2a, κ	BD
CD98	BV605	Mouse	Hamster	H202-141	IgG2a, κ	BD
CD1d	BUV563	Mouse	Rat	WTH2	IgG2a, κ	BD
Biotinylated anti-AAV8 IgG	N/A		Mouse	ADK8	IgG2a	Progen
TCRβ	APC	Mouse	Hamster	H57-597	IgG2, λ1	BD
CD200R3	APC	Mouse	Rat	Ba13	IgG2a, κ	Biolegend
Ly6G	APC	Mouse	Rat	1A8-Ly6g	IgG2a, κ	eBioscience
CD49b	APC	Mouse	Rat	DX5	IgM, κ	Biolegend
CD11b	APC	Mouse	Rat	M1/70	IgG2b, k	Biolegend
Secondary Stain						
Reagent	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
Streptavidin	PE	N/A	N/A	N/A	N/A	Biolegend
Intracellular stain						
Reagent	**Conjugate**	**Reactivity**	**Host**	**Clone**	**Isotype**	**Supplier**
Light Chain k	BV650	Mouse	Rat	187.1	IgG1, k	BD
Light Chain l	BV650	Mouse	Rat	R26-46	IgG2a, κ	BD
IgG1	BV510	Mouse	Rat	A85-1	IgG1, k	BD
IgA	FITC	Mouse	Rat	C10-3	IgG1, κ	BD

[01648] Analysis of B cell and plasma cell frequencies (**Figures 29A-29E**) and cell counts (**Figures 29F-29J**) in the bone marrow and spleen revealed that plasma cells were fully depleted in groups receiving anti-BCMAxCD3 bispecific antibody + anti-CD19/CD20 antibodies and the triple combination of anti-BCMAxCD3 bispecific antibody + efgartigimod alfa + anti-CD19/CD20 antibodies, consistent with reductions in anti-AAV8 titers seen in these groups.

However, plasma cells were incompletely depleted in anti-BCMAxCD3 bispecific antibody groups that did not also receive anti-CD19/CD20 antibodies, suggesting either that ongoing plasma cell formation is a significant contributor to the anti-AAV8 IgG antibody pool in this model, or that mice developed anti-drug antibodies that react with anti-BCMAxCD3 bispecific antibody (a human IgG) that may have limited its therapeutic effect in the absence of B cell depletion (which would also deplete anti-human IgG-specific B cells). The effectiveness of anti-CD19/CD20 antibodies-mediated B cell depletion was also confirmed in analyses of naïve, memory, and AAV-specific B cells, with all subsets fully depleted except for a small subset of total memory B cells that were not depleted in the anti-BCMAxCD3 bispecific antibody + anti-CD19/CD20 antibodies combination group. Collectively, these data show that the titer reductions observed in the anti-BCMAxCD3 bispecific antibody + efgartigimod alfa + anti-CD19/CD20 antibodies are consistent with the expected mechanism of action, and that, by comparison, incomplete titer reductions observed in the anti-BCMAxCD3 bispecific antibody + efgartigimod alfa group may be explained by incomplete plasma cell depletion, possibly due to development of anti-drug antibodies reactive with anti-BCMAxCD3 bispecific antibody, efgartigimod, or both.

Example 24: Negative impact of efgartigimod on BCMAxCD3 serum drug concentration, which is partially preventable with B cell depletion, is consistent with cross-reactive anti-drug antibody formation

[01649] Robust bone marrow plasma cell depletion was observed in BCMAxCD3, BCMAxCD3 + anti-CD19/CD20, and BCMAxCD3 + anti-CD19/CD20 + efgartigimod treatment groups that was consistent with the expected mechanism of action of BCMAxCD3 observed in previous studies (Limnander et al., 2023). However, mice treated with BCMAxCD3 + efgartigimod, but not anti-CD19/CD20, unexpectedly showed incomplete bone marrow plasma cell depletion (**Figure 29A** and **Figure 29F**). To better understand the impact of efgartigimod on the efficacy of BCMAxCD3, serum BCMAxCD3 concentrations were evaluated during the immunomodulation treatment period. Repeated injections of BCMAxCD3 in BCMAxCD3 and BCMAxCD3 + anti-CD19/20 treatment groups resulted in expected increases in serum concentrations of BCMAxCD3 (**Figure 30**). Moreover, mice treated with BCMAxCD3 + anti-CD19/20 + efgartigimod showed significantly lower levels of serum BCMAxCD3, as expected from the mechanism of action of efgartigimod, which blocks FcRn-mediated recycling of IgG, including recycling of therapeutic IgGs such as BCMAxCD3. However, mice receiving BCMAxCD3 + efgartigimod without anti-CD19/20 exhibited an even greater rate of BCMAxCD3

antibody clearance that resulted in complete loss of BCMAxCD3 in serum starting 13 days after the initial efgartigimod dose (**Figure 30**).

[01650] A faster clearance rate, reversible with B cell depletion, suggests that a humoral immune response may be contributing to drug clearance via development of anti-drug antibodies. Efgartigimod is a human IgG1 antibody fragment and is known to be immunogenic in mice. BCMAxCD3 is a human IgG4, which possesses >90% sequence identity to hIgG1. Therefore, it was concluded that efgartigimod, in the absence of additional B cell depletion, induced human IgG1/IgG4 cross-reactive anti-drug antibodies that accelerated BCMAxCD3 clearance. It was further concluded that this anti-drug antibody response, in the absence of additional B cell depletion, negatively impacted BCMA-mediated bone marrow plasma cell depletion and consequently AAV titer reductions. Thus, the contribution of anti-CD19/20 antibodies to the efficacy of BCMAxCD3 in non-human systems, in the presence of efgartigimod, may be model-specific through prevention of a xenogeneic anti-drug antibody response.

Example 25: Plasma cell depletion in combination with neonatal Fc receptor (FcRn) blockade potently reduces naturally-occurring AAV titers in AAV-seropositive cynomolgus macaques

[01651] To evaluate whether plasma cell depletion with BCMAxCD3 could similarly suppress naturally-occurring AAV titers arising from exposure to wild-type AAVs, as is common in humans, a non-human primate study was initiated with AAV8-seropositive macaques. Macaques were divided by AAV neutralizing antibody (nAb) titer into five treatment groups (n=3-5 each), each containing animals of high nAb titer (> 1:450), as well as one group of seronegative control animals (n=3). Subsequently, animals were treated with various combinations of a plasma cell-depleting bispecific BCMAxCD3 antibody (REGN5458, 20 mg/kg weekly), a B cell-depleting bispecific CD20xCD3 antibody (REGN1979, 0.1 mg/kg on Study Day 1, 1mg/kg on Study Day 4, 8, and weekly thereafter), and/or an FcRn blocker (efgartigimod, 20 mg/kg on Study Day 11,12,13, 20, and 27). Efgartigimod dosing was delayed relative to REGN5458 and REGN1979 dosing to minimize the impact of efgartigimod on REGN5458 and REGN1979 drug half-life due to FcRn blockade and/or cross-reactive anti-drug antibody development. NAb titers were analyzed weekly by cell-based neutralization assay, conducted by VRL Diagnostics (San Antonio, Texas). A schematic of the study design is shown is **Figure 31**.

[01652] Longitudinal analysis of NAb titers revealed that only groups treated with immunomodulation cocktails containing REGN5458 showed substantive geometric mean titer

reductions by ~4 weeks after the start of immunomodulation. Whereas macaques receiving REGN5458-containing cocktails showed titer reductions of >10-fold, macaques receiving a cocktail containing efgartigimod and REGN1979, but not REGN5458, showed only marginal geometric mean nAb titer reduction of ~2-fold (**Figure 32A**). Similar to findings in mice, cocktails containing both a plasma cell depleter (REGN5458) and an FcRn blocker (efgartigimod), or all three immunomodulators, elicited the greatest titer reductions, with the triple combination of REGN5458, REGN1979, and efgartigimod inducing a >100-fold reduction in nAb titer (**Figure 32A**). On Study Day 29, two animals in the triple combination group exhibited nAb titers below the limit of detection of the assay (**Figure 32B**), suggesting that these animals could be successfully dosed with an AAV vector. Thus, plasma cell depletion is an effective strategy for suppressing naturally-occurring anti-AAV antibody titers, even of high-titer, to a level that is compatible with AAV dosing.

Example 26: Prophylactic CD40 blockade with anti-CD40 mAb suppresses the IgM, IgG, and neutralizing antibody (NAb) response to AAV in non-human primates.

[01653] As demonstrated in Examples 12-13, prophylactic CD40 blockade with anti-CD40 mAb potently suppresses anti-AAV antibody responses and enables systemic AAV vector re-administration in mice. To evaluate the ability of CD40 blockade to suppress antibody responses to AAV vectors in larger mammals, a similar study was conducted in cynomolgus macaques. Specifically, AAV8-seronegative cynomolgus macaques were divided into groups of 4-6 animals receiving either no immunomodulation (Groups 1 and 2) or the anti-CD40 antagonist mAb (Group 3; COMP11209, 50mg/kg i.v.). After three initial loading doses of anti-CD40 mAb on Study Days -7, -3, and 1, animals in Groups 2 and 3 were dosed intravenously on Study Day 1 with an AAV8 vector ("AAV #1") encoding eGFP at 1e13 vector genomes per kilogram (vg/kg). Animals in Group 3 continued to receive anti-CD40 mAb weekly at the same dose until Study Day 76. Blood was sampled periodically for longitudinal antibody titer analysis. A schematic of the study design is shown in **Figure 33**.

[01654] Analysis of serum anti-AAV IgM, IgG, and neutralizing antibody (NAb) titers was conducted by anti-AAV IgM / IgG titer ELISA and cell-based neutralization assay, according to standard methods utilized by the University of Pennsylvania Gene Therapy Program Immunology Core. Results indicated that, as expected, macaques receiving no antibody (Group 2, "No immunomodulation") mounted robust anti-AAV8 IgM, IgG, and NAb responses in the weeks following AAV exposure that were sustained in most animals for the entire ~10 week sampling period (**Figures 34A,-C**). By contrast, anti-CD40 mAb-treated animals showed

significantly reduced antibody responses, exhibiting only transient IgM, IgG, and NAb responses that were lower in magnitude and waned to undetectable or near-undetectable levels over the course of the ~10 week sampling period. By Study Day 71 anti-CD40 mAb-treated animals, but not control animals, recorded geometric mean titers below the limit of detection (**Figures 34D-F**). Thus, these data show that antibody-mediated CD40 blockade is an effective strategy to suppress the magnitude and duration of anti-AAV8 antibody responses following AAV vector treatment in non-human primates.

Example 27: Prophylactic CD40 blockade with anti-CD40 mAb enables systemic AAV re-dosing in non-human primates.

[01655] In this Example, the ability of anti-CD40 mAb-treatment to enable systemic AAV vector re-administration was evaluated. All animals from Example 26, including those that had not previously received AAV #1 (Group 1), were intravenously administered a second AAV8 vector, ("AAV #2") encoding a secreted human IgG1 monoclonal antibody transgene from a liver-specific promoter, at 1e13 vg/kg on Study Day 76. Four weeks later (Study Day 104), animals were necropsied, and liver transduction was evaluated by digital PCR. As expected, few vector genomes were detected in control animals that previously received AAV #1 but no immunomodulation (**Figure 35A**). By contrast, anti-CD40 mAb-treated animals showed evidence of strong transduction with the second AAV vector, exhibiting vector genome levels approaching that of Group 1 transduction control animals that received AAV #2 only. Analysis of transgene RNA (by Taqman RT-qPCR) (**Figure 35B**) and serum transgene protein (by hIgG1 ELISA) (**Figure 35C**) showed similar findings, with anti-CD40 mAb-treated animals, but not re-dosed animals receiving no antibody, exhibiting readily detectable levels of transgene RNA and serum hIgG1 protein. Thus, these findings show that systemic AAV vector re-administration is achievable via prophylactic antibody-mediated CD40 blockade in non-human primates.

Example 28: Prophylactic CD40 blockade with anti-CD40 mAb reduces liver injury associated with anti-transgene T cell responses, and results in increased transgene expression in non-human primates.

[01656] T cell responses to transgene and AAV capsid have previously been shown to be associated with liver injury and loss of transgene expression in liver-directed AAV gene therapies (Gao et al 2009; Manno et al 2006). To evaluate whether CD40 blockade can mitigate T cell-mediated liver injury post AAV treatment, cynomolgus macaques from Examples 26-27 were longitudinally evaluated for alanine aminotransferase activity (ALT) in serum, a common

clinical measurement of liver injury. As expected, AAV #1, which encoded the immunogenic transgene eGFP, resulted in transient ALT elevations in control animals treated with AAV but not antibody (**Figure. 36A**), as has previously been observed (Gao et al 2009). In contrast, anti-CD40 mAb-treated animals showed lower average ALT levels following AAV #1 dosing. Moreover, consistent with a reduced T cell response, at the time of necropsy on Study Day 104, anti-CD40 mAb-treated animals exhibited higher mean levels of AAV #1 vector genomes and eGFP RNA compared to control animals that did not receive anti-CD40 mAb (**Figures 36B-C**). Thus, these data suggest that anti-CD40 mAb blockade is an effective strategy to attenuate liver injury and transgene loss associated with anti-transgene T cell immune responses post AAV dosing.

Example 29: Use of anti-CD40 antagonist antibodies to prevent an immune response to IgG degrading enzyme (IdeS), and therefore enable repeated IdeS and AAV dosing.

[01657] The IgG degrading enzyme IdeS has previously been shown to transiently reduce anti-AAV IgG through IgG cleavage (Leborgne et al., 2020). Treatment of animals with IdeS *in vivo* has emerged as a promising strategy to transiently deplete anti-AAV IgGs in circulation, thereby in some cases, enabling AAV transduction, and in some cases, re-transduction. However, because IdeS is of bacterial origin, and therefore immunogenic, the ability to re-dose IdeS to enable repeated rounds of AAV dosing in seropositive subjects remains unclear.

[01658] In this Example, anti-CD40 antagonist antibodies are administered to AAV8-seropositive cynomolgus macaques prior to IdeS administration to prevent an antibody response to IdeS. The CD40 antibodies are resistant to IdeS cleavage (e.g., through use of an engineered antibody isotype that carries mutations within the known cleavage site of IdeS (e.g., within the CH2 hinge amino acid sequence CPAPELLGGPSVF (SEQ ID NO: 1117)) or by swapping this sequence with the homologous sequence in another IdeS-resistant species such as mouse) and therefore maintain efficacy in the presence of IdeS. The administration of IdeS results in cleavage of circulating IgGs, including anti-AAV8 IgGs. Analysis of anti-AAV8 IgGs and neutralizing antibodies 2-4 days later confirms that IdeS effectively reduced anti-AAV8 IgGs to levels that are below neutralizing levels. An AAV8 vector is subsequently dosed, and transduction is measured at some time post dosing (e.g., for a secreted lysosomal enzyme transgene such as anti-CD63 scFv:GAA, 1-2 weeks later in blood by ELISA). Analysis of anti-IdeS titers 2-4 weeks after IdeS dosing confirms suppression of antibody response to IdeS. At some time after the first AAV (e.g., 2 months later), at a time when the animals are confirmed to be AAV seropositive again (due to the transient nature of IdeS activity), anti-CD40 antibodies

are again administered, followed by IdeS. Once again, 2-4 days later, analysis of anti-AAV8 IgGs and neutralizing antibodies confirms that IdeS effectively reduced anti-AAV8 IgGs to below neutralizing levels. A second AAV8 vector is subsequently dosed, and transduction is measured at some time post dosing (e.g., for a human Factor IX transgene, 1-4 weeks later in blood by ELISA). Analysis of anti-IdeS titers 2-4 weeks after the second IdeS dosing confirms suppression of antibody response to IdeS. Additional AAVs can be re-administered, as long as IdeS is administered prior to dosing, and as long as anti-CD40 antibodies are administered prior to IdeS administration to prevent an antibody response to IdeS.

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Table 41: Informal Sequence Listing

SEQ ID NO	Sequence	Description
1	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAAC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTAGTG GTACTATTGGTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC TCTAGAGACAATTCCAAGAACACGCTCTATCTGCAAATGAACAGCCTGAGAGG CGAGGACACGGCCGTTTATTACTGTGCGAAAGATACGGAAAGGGATATAACT GGATCTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCA	30027P2 HCVR nucleic acid sequence
2	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGTI GKTYYADSVKGRFTISRDNSKNTLYLQMNSLRGEDTAVYYCAKDTERDITGSPFDY WGQGTLVTVSS	30027P2 HCVR amino acid sequence
3	GGATTCACCTTTAGCAGCTATGCC	30027P2 HCDR1 nucleic acid sequence
4	GFTFSSYA	30027P2 HCDR1 amino acid sequence
5	ATTAGTGGTACTATTGGTAAGACA	30027P2 HCDR2 nucleic acid sequence
6	ISGTIGKT	30027P2 HCDR2 amino acid sequence
7	GCGAAAGATACGGAAAGGGATATAACTGGATCTCCTTTTGACTAC	30027P2 HCDR3 nucleic acid sequence
8	AKDTERDITGSPFDY	30027P2 HCDR3 amino acid sequence
9	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTT GCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTC ACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAA CAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT TAAA	Common LCVR nucleic acid sequence
10	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK	Common LCVR amino acid sequence
11	CAGAGCATTAGCAGCTAT	Common LCDR1 nucleic acid sequence
12	QSISSY	Common LCDR1 amino acid sequence
13	GCTGCATCC	Common LCDR2 nucleic acid sequence
14	AAS	Common LCDR2 amino acid sequence
15	CAACAGAGTTACAGTACCCCTCCGATCACC	Common LCDR3 nucleic acid sequence
16	QQSYSTPPIT	Common LCDR3 amino acid sequence

17	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAAC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTAGTG GTACTATTGGTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC TCTAGAGACAATTCCAAGAACACGCTCTATCTGCAAATGAACAGCCTGAGAGG CGAGGACACGGCCGTTTATTACTGTGCGAAAGATACGGAAAGGGATATAACT GGATCTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCC TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT GACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC TCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAG CAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCAC CGTGCCCAGCACCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCCAAAAC CCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTG GACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCG TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCAC GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAA ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCC CCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA AAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC GGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT TCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGT CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTC CCTCTCCCTGTCTCTGGGTAAATGA	30027P2 heavy chain nucleic acid sequence
18	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGTI GKTYYADSVKGRFTISRDNSKNTLYLQMNSLRGEDTAVYYCAKDTERDITGSPFDY WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK	30027P2 heavy chain amino acid sequence
19	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGA GTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTAT CAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTT GCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTC ACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAA CAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGAT TAAACGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCA GTTGAAATCTGGAACTGCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAG AGAGGCCAAAGTACAGTGGAAGGTGGATAACGCCCTCCAATCGGGTAACTCC CAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTACAGCCTCAGCA GCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTG CGAAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGG GAGAGTGTTAG	Common light chain nucleic acid sequence
20	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Common light chain amino acid sequence

21	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAGGCCTTCGGAGACCC TGTCACTCACTTGTAGTGTCTCTGGTGCCTCCATGAACACTAATAATTACTATTG GGGCTGGATCCGCCAGCCCCCCGGGAAGGGTCTGGAGTGGATTGGGAGTGG CTATTATAATGGGAACACCTACTATAATCCGTCTCTCAAGAGTCGAGTCACCAT ATCTGTTGACACGTCCAAGAACCAGTTCTCCCTGAAGTTGAATTCTGTGACCGC CGCAGATACGGCTGTGTATTATTGTGCGAGACAGACCCCCCCTCGTATAATTG GAAGTCCGAATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCA	21519P2 HCVR nucleic acid sequence
22	QLQLQESGPGLVRPSETLSLTCSVSGASMNTNNYYWGWIRQPPGKGLEWIGSGY YNGNTYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARQTPPRIIGSPNI WGQGTMVTVSS	21519P2 HCVR amino acid sequence
23	GGTGCCTCCATGAACACTAATAATTACTAT	21519P2 HCDR1 nucleic acid sequence
24	GASMNTNNYY	21519P2 HCDR1 amino acid sequence
25	GGCTATTATAATGGGAACACC	21519P2 HCDR2 nucleic acid sequence
26	GYYNGNT	21519P2 HCDR2 amino acid sequence
27	GCGAGACAGACCCCCCCTCGTATAATTGGAAGTCCGAATATC	21519P2 HCDR3 nucleic acid sequence
28	ARQTPPRIIGSPNI	21519P2 HCDR3 amino acid sequence
29	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAGGCCTTCGGAGACCC TGTCACTCACTTGTAGTGTCTCTGGTGCCTCCATGAACACTAATAATTACTATTG GGGCTGGATCCGCCAGCCCCCCGGGAAGGGTCTGGAGTGGATTGGGAGTGG CTATTATAATGGGAACACCTACTATAATCCGTCTCTCAAGAGTCGAGTCACCAT ATCTGTTGACACGTCCAAGAACCAGTTCTCCCTGAAGTTGAATTCTGTGACCGC CGCAGATACGGCTGTGTATTATTGTGCGAGACAGACCCCCCCTCGTATAATTG GAAGTCCGAATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCC ACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGA GAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA CGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCG TGCCCAGCACCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCCAAAACCC AAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGA CGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTG GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGT ACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAAC CATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCC CATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA AGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCT TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCC TCTCCCTGTCTCTGGGTAAATGA	21519P2 heavy chain nucleic acid sequence

30	QLQLQESGPGLVRPSETLSLTCSVSGASMNTNNYYWGWIRQPPGKGLEWIGSGY YNGNTYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARQTPPRIIGSPNI WGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK	21519P2 heavy chain amino acid sequence
31	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGGCAGCTATGGCATGGCG TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTG GTAGTGGTGATTATACAAACTACGCAGACTCCGTGAAGCGCCGGTTCACCATC TCCAGAGACAATTCCAAGAACACGCTTTATCTACAAATGAGCAGCCTGAGAGC CGAGGACACGGCCGTATATTACTGTGCGAAAGAGAAGACTGGAACGACGGGC TATTTGTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCA	21520P2 HCVR nucleic acid sequence
32	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYGMAWVRQAPGKGLEWVSAISGS GDYTNYADSVKRRFTISRDNSKNTLYLQMSSLRAEDTAVYYCAKEKTGTTGYLYSG MDVWGQGTTVTVSS	21520P2 HCVR amino acid sequence
33	GGATTCACCTTTGGCAGCTATGGC	21520P2 HCDR1 nucleic acid sequence
34	GFTFGSYG	21520P2 HCDR1 amino acid sequence
35	ATTAGTGGTAGTGGTGATTATACA	21520P2 HCDR2 nucleic acid sequence
36	ISGSGDYT	21520P2 HCDR2 amino acid sequence
37	GCGAAAGAGAAGACTGGAACGACGGGCTATTTGTACTCCGGTATGGACGTC	21520P2 HCDR3 nucleic acid sequence
38	AKEKTGTTGYLYSGMDV	21520P2 HCDR3 amino acid sequence

39	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGGCAGCTATGGCATGGCG TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTG GTAGTGGTGATTATACAAACTACGCAGACTCCGTGAAGCGCCGGTTCACCATC TCCAGAGACAATTCCAAGAACACGCTTTATCTACAAATGAGCAGCCTGAGAGC CGAGGACACGGCCGTATATTACTGTGCGAAAGAGAAGACTGGAACGACGGGC TATTTGTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG CACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC CGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACA AGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCC ATGCCCACCGTGCCCAGCACCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCC CCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCG TGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGT GGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTT CAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGC TGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCC ATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGT ACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACC TGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCA ATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGA CGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGG AGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTAC ACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA	21520P2 heavy chain nucleic acid sequence
40	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYGMAWVRQAPGKGLEWVSAISGS GDYTNYADSVKRRFTISRDNSKNTLYLQMSSLRAEDTAVYYCAKEKTGTTGYLYSG MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR VESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQ KSLSLSLGK	21520P2 heavy chain amino acid sequence

41	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAGGCCTTCGGAGACCC TGTCACTCACTTGTAGTGTCTCTGGTGCCTCCATGAACACTAATAATTACTATTG GGGCTGGATCCGCCAGCCCCCCGGGAAGGGTCTGGAGTGGATTGGGAGTGG CTATTATAATGGGAACACCTACTATAATCCGTCTCTCAAGAGTCGAGTCACCAT ATCTGTTGACACGTCCAAGAACCAGTTCTCCCTGAAGTTGAATTCTGTGACCGC CGCAGATACGGCTGTGTATTATTGTGCGAGACAGACCCCCCCTCGTATAATTG GAAGTCCGAATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCC ACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGA GAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA CGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCG TGCCCAGCACCAGGCGGTGGCGGACCATCAGTCTTCCTGTTCCCCCCAAAACC CAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGG ACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGT GGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCAC GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAA ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCC CCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA AAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC GGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT TCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGT CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTC CCTCTCCCTGTCTCTGGGTAAATGA	REGN16334 D1 heavy chain nucleic acid sequence
42	QLQLQESGPGLVRPSETLSLTCSVSGASMNTNNYYWGWIRQPPGKGLEWIGSGY YNGNTYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARQTPPRIIGSPNI WGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPGGGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK	REGN16334 D1 heavy chain amino acid sequence

43	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGGCAGCTATGGCATGGCG TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTG GTAGTGGTGATTATACAAACTACGCAGACTCCGTGAAGCGCCGGTTCACCATC TCCAGAGACAATTCCAAGAACACGCTTTATCTACAAATGAGCAGCCTGAGAGC CGAGGACACGGCCGTATATTACTGTGCGAAAGAGAAGACTGGAACGACGGGC TATTTGTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCTCTACAAAGGGACCTTCTGTGTTTCCTCTGGCTCCTTGTTCTAGATCT ACATCTGAATCTACAGCTGCTCTGGGATGTCTGGTGAAGGATTATTTTCCTGAA CCTGTGACAGTGTCTTGGAATTCTGGAGCTCTGACATCTGGAGTGCATACATTT CCTGCTGTGCTGCAGTCTTCTGGACTGTATTCTCTGTCTTCTGTGGTGACAGTG CCTTCTTCTTCTCTGGGAACAAAGACATATACATGTAATGTGGATCATAAGCCT TCTAATACAAAGGTGGATAAGAGAGTGGAATCTAAGTATGGACCTCCTTGTCC TCCTTGTCCTGCTCCTGGCGGTGGCGGACCTTCTGTGTTTCTGTTTCCTCCTAAG CCTAAGGATACACTGATGATCTCTAGAACACCTGAAGTGACATGTGTGGTGGT GGATGTGTCTCAGGAAGATCCTGAAGTGCAGTTTAATTGGTATGTGGATGGA GTGGAAGTGCATAATGCTAAGACAAAGCCTAGAGAAGAACAGTTTAATTCTAC ATATAGAGTGGTGTCTGTGCTGACAGTGCTGCATCAGGATTGGCTGAATGGAA AGGAATATAAGTGTAAGGTGTCTAATAAGGGACTGCCTTCTTCTATCGAAAAG ACAATCTCTAAGGCTAAGGGACAGCCTAGAGAACCTCAGGTGTATACACTGCC TCCTTCTCAGGAAGAAATGACAAAGAATCAGGTGTCTCTGACATGTCTGGTGA AGGGATTTTATCCTTCTGATATCGCTGTGGAATGGGAATCTAATGGACAGCCT GAAAATAATTATAAGACAACACCTCCTGTGCTGGATTCTGATGGATCTTTTTTT CTGTATTCTAGACTGACAGTGGATAAGTCTAGATGGCAGGAAGGAAATGTGTT TTCTTGTTCTGTGATGCATGAAGCTCTGCATAATAGATTTACACAGAAGTCTCT GTCTCTGTCTCCTGGAAAGTAG	REGN16334 and REGN16335 D2 heavy chain nucleic acid sequence
44	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYGMAWVRQAPGKGLEWVSAISGS GDYTNYADSVKRRFTISRDNSKNTLYLQMSSLRAEDTAVYYCAKEKTGTTGYLYSG MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR VESKYGPPCPPCPAPGGGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNRFT QKSLSLSPGK	REGN16334 and REGN16335 D2 heavy chain amino acid sequence

45	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAAC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTAGTG GTACTATTGGTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC TCTAGAGACAATTCCAAGAACACGCTCTATCTGCAAATGAACAGCCTGAGAGG CGAGGACACGGCCGTTTATTACTGTGCGAAAGATACGGAAAGGGATATAACT GGATCTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCC TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT GACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC TCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAG CAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCAC CGTGCCCAGCACCAGGCGGTGGCGGACCATCAGTCTTCCTGTTCCCCCCAAAA CCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGT GGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGC GTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGC ACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGG CAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGA AAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCT GCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTG GTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGC AGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCC TTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGA ATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGA AGTCCCTCTCCCTGTCTCTGGGTAAATGA	REGN16335 D1 heavy chain nucleic acid sequence
46	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGTI GKTYYADSVKGRFTISRDNSKNTLYLQMNSLRGEDTAVYYCAKDTERDITGSPFDY WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPGGGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK	REGN16335 D1 heavy chain amino acid sequence

47	CAGCTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAGGCCTTCGGAGACCC TGTCACTCACTTGTAGTGTCTCTGGTGCCTCCATGAACACTAATAATTACTATTG GGGCTGGATCCGCCAGCCCCCCGGGAAGGGTCTGGAGTGGATTGGGAGTGG CTATTATAATGGGAACACCTACTATAATCCGTCTCTCAAGAGTCGAGTCACCAT ATCTGTTGACACGTCCAAGAACCAGTTCTCCCTGAAGTTGAATTCTGTGACCGC CGCAGATACGGCTGTGTATTATTGTGCGAGACAGACCCCCCCTCGTATAATTG GAAGTCCGAATATCTGGGGCCAAGGGACAATGGTCACCGTCTCTTCAGCCTCC ACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCCGA GAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGTGA CGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCGGCT GTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCC AGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAGCA ACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCACCG TGCCCAGCACCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCCAAAACCC AAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTGGA CGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCGTG GAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCACGT ACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCAAG GAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAAAC CATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCCCC CATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA AGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTC CTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGTCT TCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTCCC TCTCCCTGTCTCTGGGTAAATGA	REGN16431 D1 heavy chain nucleic acid sequence
48	QLQLQESGPGLVRPSETLSLTCSVSGASMNTNNYYWGWIRQPPGKGLEWIGSGY YNGNTYYNPSLKSRVTISVDTSKNQFSLKLNSVTAADTAVYYCARQTPPRIIGSPNI WGQGTMVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK	REGN16431 D1 heavy chain amino acid sequence

49	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGGCAGCTATGGCATGGCG TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTG GTAGTGGTGATTATACAAACTACGCAGACTCCGTGAAGCGCCGGTTCACCATC TCCAGAGACAATTCCAAGAACACGCTTTATCTACAAATGAGCAGCCTGAGAGC CGAGGACACGGCCGTATATTACTGTGCGAAAGAGAAGACTGGAACGACGGGC TATTTGTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCTCTACAAAGGGACCTTCTGTGTTTCCTCTGGCTCCTTGTTCTAGATCT ACATCTGAATCTACAGCTGCTCTGGGATGTCTGGTGAAGGATTATTTTCCTGAA CCTGTGACAGTGTCTTGGAATTCTGGAGCTCTGACATCTGGAGTGCATACATTT CCTGCTGTGCTGCAGTCTTCTGGACTGTATTCTCTGTCTTCTGTGGTGACAGTG CCTTCTTCTTCTCTGGGAACAAAGACATATACATGTAATGTGGATCATAAGCCT TCTAATACAAAGGTGGATAAGAGAGTGGAATCTAAGTATGGACCTCCTTGTCC TCCTTGTCCTGCTCCTCCTGTGGCTGGACCTTCTGTGTTTCTGTTTCCTCCTAAG CCTAAGGATACACTGATGATCTCTAGAACACCTGAAGTGACATGTGTGGTGGT GGATGTGTCTCAGGAAGATCCTGAAGTGCAGTTTAATTGGTATGTGGATGGA GTGGAAGTGCATAATGCTAAGACAAAGCCTAGAGAAGAACAGTTTAATTCTAC ATATAGAGTGGTGTCTGTGCTGACAGTGCTGCATCAGGATTGGCTGAATGGAA AGGAATATAAGTGTAAGGTGTCTAATAAGGGACTGCCTTCTTCTATCGAAAAG ACAATCTCTAAGGCTAAGGGACAGCCTAGAGAACCTCAGGTGTATACACTGCC TCCTTCTCAGGAAGAAATGACAAAGAATCAGGTGTCTCTGACATGTCTGGTGA AGGGATTTTATCCTTCTGATATCGCTGTGGAATGGGAATCTAATGGACAGCCT GAAAATAATTATAAGACAACACCTCCTGTGCTGGATTCTGATGGATCTTTTTTT CTGTATTCTAGACTGACAGTGGATAAGTCTAGATGGCAGGAAGGAAATGTGTT TTCTTGTTCTGTGATGCATGAAGCTCTGCATAATAGATTTACACAGAAGTCTCT GTCTCTGTCTCCTGGAAAGTAG	REGN16431 and REGN16432 D2 heavy chain nucleic acid sequence
50	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYGMAWVRQAPGKGLEWVSAISGS GDYTNYADSVKRRFTISRDNSKNTLYLQMSSLRAEDTAVYYCAKEKTGTTGYLYSG MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR VESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQ FNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGL PSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNRFTQ KSLSLSPGK	REGN16431 and REGN16432 D2 heavy chain amino acid sequence

51	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAAC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTAGTG GTACTATTGGTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC TCTAGAGACAATTCCAAGAACACGCTCTATCTGCAAATGAACAGCCTGAGAGG CGAGGACACGGCCGTTTATTACTGTGCGAAAGATACGGAAAGGGATATAACT GGATCTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCC TCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAGCACCTCC GAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCGAACCGGT GACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCC TCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACAAGCCCAG CAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCCATGCCCAC CGTGCCCAGCACCACCTGTGGCAGGACCATCAGTCTTCCTGTTCCCCCCAAAAC CCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGCGTGGTGGTG GACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACGTGGATGGCG TGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTTCAACAGCAC GTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAACGGCA AGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTCCATCGAGAAA ACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTGTACACCCTGCC CCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCA AAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCC GGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCT TCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAGGAGGGGAATGT CTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACACAGAAGTC CCTCTCCCTGTCTCTGGGTAAATGA	REGN16432 D1 heavy chain nucleic acid sequence
52	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGTI GKTYYADSVKGRFTISRDNSKNTLYLQMNSLRGEDTAVYYCAKDTERDITGSPFDY WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLS LSLGK	REGN16432 D1 heavy chain amino acid sequence
53	PEPPTACREKQYLINSQCCSLCQPGQKLVSDCTEFTETECLPCGESEFLDTWNRET HCHQHKYCDPNLGLRVQQKGTSETDTICTCEEGWHCTSEACESCVLHRSCSPGFG VKQIATGVSDTICEPCPVGFFSNVSSAFEKCHPWTSCETKDLVVQQAGTNKTDVV CGPQDRLREQKLISEEDLGGEQKLISEEDLHHHHHH	REGN3094 (human CD40 extracellular domain with C-terminal MMH tag; "hCD40-MMH")
54	PEPPTACREKQYLINSQCCSLCQPGQKLVSDCTEFTETECLPCGESEFLDTWNRETR CHQHKYCDPNLGLRVQQKGTSETDTICTCEEGLHCTSESCESCVPHRSCLPGFGVK QIATGVSDTICEPCPVGFFSNVSSAFEKCRPWTSCETKDLVVQQAGTNKTDVVCG PQDRQREQKLISEEDLGGEQKLISEEDLHHHHHH	REGN3097 (monkey CD40 extracellular domain with C-terminal MMH tag; "mfCD40-MMH")
55	LGQCVTCSDKQYLHDGQCCDLCQPGSRLTSHCTALEKTQCHPCDSGEFSAQWNR EIRCHQHRHCEPNQGLRVKKEGTAESDTVCTCKEGQHCTSKDCEACAQHTPCIPG FGVMEMATETTDTVCHPCPVGFFSNQSSLFEKCYPWTSCEDKNLEVLQKGTSQT NVICGLKSRMREQKLISEEDLGGEQKLISEEDLHHHHHH	REGN3098 (mouse CD40 extracellular domain with C-terminal MMH tag; "mCD40-MMH")

56	PEPPTACREKQYLINSQCCSLCQPGQKLVSDCTEFTETECLPCGESEFLDTWNRET HCHQHKYCDPNLGLRVQQKGTSETDTICTCEEGWHCTSEACESCVLHRSCSPGFG VKQIATGVSDTICEPCPVGFFSNVSSAFEKCHPWTSCETKDLVVQQAGTNKTDVV CGPQDRLREPRGPTIKPCPPCKCPAPNLLGGPSVFIFPPKIKDVLMISLSPIVTCVVV DVSEDDPDVQISWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGK EFKCKVNNKDLPAPIERTISKPKGSVRAPQVYVLPPPEEEMTKKQVTLTCMVTDF MPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKLRVEKKNWVERNSYSCS VVHEGLHNHHTTKSFSRTPGK	REGN3095 (hCD40-mFc)
57	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY EESNRYHADSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDY WGQGTLVTVSS	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] HCVR amino acid sequence
58	SYGMH	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] HCDR1 amino acid sequence
59	VISYEESNRYHADSVKG	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] HCDR2 amino acid sequence
60	DGGIAAPGPDY	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] HCDR3 amino acid sequence
61	DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQVLISLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIR	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] LCVR amino acid sequence
62	RSSQSLLYSNGYNYLD	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] LCDR1 amino acid sequence
63	LGSNRAS	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] LCDR2 amino acid sequence
64	MQARQTPFT	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] LCDR3 amino acid sequence
65	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY EESNRYHADSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	Iscalimab [CFZ533] heavy chain amino acid sequence

66	DIVMTQSPLSLTVTPGEPASISCRSSQSLLYSNGYNYLDWYLQKPGQSPQVLISLGS NRASGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQARQTPFTFGPGTKVDIR RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Iscalimab [CFZ533] and lucatumumab [HCD122 and CHIR-12.12] light chain amino acid sequence
67	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSG RGNIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQ GTTVTVSS	Ravagalimab [ABBV-323]/Ab102] and Ab101 HCVR amino acid sequence
68	GFTFSDYGMN	Ravagalimab [ABBV-323]/Ab102] and Ab101 HCDR1 amino acid sequence
69	YISSGRGNIYYADTVKG	Ravagalimab [ABBV-323]/Ab102] and Ab101 HCDR2 amino acid sequence
70	SWGYFDV	Ravagalimab [ABBV-323]/Ab102] and Ab101 HCDR3 amino acid sequence
71	DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNQKNYLTWFQQKPGQPPKLLIY WASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGQGTKLE IK	Ravagalimab [ABBV-323]/Ab102] and Ab101 LCVR amino acid sequence
72	KSSQSLLNRGNQKNYLT	Ravagalimab [ABBV-323]/Ab102] and Ab101 LCDR1 amino acid sequence
73	WASTRES	Ravagalimab [ABBV-323]/Ab102] and Ab101 LCDR2 amino acid sequence
74	QNDYTYPLT	Ravagalimab [ABBV-323]/Ab102, BI-655064, Ab101, Antibody A and Antibody B LCDR3 amino acid sequence
75	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSG RGNIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQ GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDQLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVLHEALHNHYTQKSLSLS PGK	Ravagalimab [ABBV-323] /Ab102 heavy chain amino acid sequence
76	DIVMTQSPDSLAVSLGERATINCKSSQSLLNRGNQKNYLTWFQQKPGQPPKLLIY WASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGQGTKLE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Ravagalimab [ABBV-323]/Ab102 and Ab101 light chain amino acid sequence
77	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDY WGQGTLVTVSS	BI-655064 and Antibody B HCVR amino acid sequence
78	GFTFSDYGMH	BI-655064 HCDR1 amino acid sequence
79	YISSGNRIIYYADTVKG	BI-655064, Antibody A and Antibody B HCDR2 amino acid sequence

80	QDGYRYAMDY	BI-655064, Antibody A and Antibody B HCDR3 amino acid sequence
81	DIVMTQSPDSLAVSLGEKVTINCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIY WTSTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVE IK	BI-655064 and Antibody B LCVR amino acid sequence
82	KSSQSLLNSGNQKNYLT	BI-655064, Antibody A and Antibody B LCDR1 amino acid sequence
83	WTSTRES	BI-655064, Antibody A and Antibody B LCDR2 amino acid sequence
84	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK	BI-655064 and Antibody B heavy chain amino acid sequence
85	DIVMTQSPDSLAVSLGEKVTINCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIY WTSTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	BI-655064 and Antibody B light chain amino acid sequence
86	QLQLQESGPGLLKPSETLSLTCTVSGGSISSPGYYGGWIRQPPGKGLEWIGSIYKSG STYHNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCTRPVVRYFGWFDPWG QGTLVTVSS	Bleselumab HCVR amino acid sequence
87	GGSISSPGYY	Bleselumab HCDR1 amino acid sequence
88	IYKSGST	Bleselumab HCDR2 amino acid sequence
89	RPVVRYFGWFDP	Bleselumab HCDR3 amino acid sequence
90	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASNLESG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPTFGQGTKVEIK	Bleselumab LCVR amino acid sequence
91	QGISSA	Bleselumab LCDR1 amino acid sequence
92	DAS	Bleselumab LCDR2 amino acid sequence
93	QQFNSYPT	Bleselumab LCDR3 amino acid sequence
94	QLQLQESGPGLLKPSETLSLTCTVSGGSISSPGYYGGWIRQPPGKGLEWIGSIYKSG STYHNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCTRPVVRYFGWFDPWG QGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG K	Bleselumab heavy chain amino acid sequence

95	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPKLLIYDASNLESG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQFNSYPTFGQGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Bleselumab light chain amino acid sequence
96	QVKLEESGPGLVAPSQSLSITCTVSGFSLSRYSVYWVRQPPGKGLEWLGMMWGG GSTDYNSALKSRLSISKDTSKSQVFLKMNSLRTDDTAMYYCVRTDGDYWGQGTSV TVSS	ch5D12 HCVR amino acid sequence
97	GFSLSRY	ch5D12 and PG102/FFP104 HCDR1 amino acid sequence
98	WGGGS	ch5D12 HCDR2 amino acid sequence
99	TDGDY	ch5D12 and PG102/FFP104 HCDR3 amino acid sequence
100	ELQLTQSPLSLPVSLGDQASISCRSSQSLVNSNGNTYLHWYLQKPGQSPKLLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCSQSTHVPWTFGGGTKLEIKR	ch5D12 LCVR amino acid sequence
101	RSSQSLVNSNGNTYLH	ch5D12 LCDR1 amino acid sequence
102	KVSNRFS	ch5D12 and PG102/FFP104 LCDR2 amino acid sequence
103	SQSTHVPWT	ch5D12 and PG102/FFP104 LCDR3 amino acid sequence
104	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISY EESNRYHADSVKGRFTISRDNSKITLYLQMNSLRTEDTAVYYCARDGGIAAPGPDY WGQGTLVTVSSASTKGPSVFPLAPASKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	Lucatumumab [HCD122 and CHIR-12.12] heavy chain amino acid sequence
105	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPG DSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGTAAGRDYYYYY GMDVWGQGTTVTVSS	CHIR-5.9 HCVR amino acid sequence
106	AIVMTQPPLSSPVTLGQPASISCRSSQSLVHSDGNTYLNWLQQRPGQPPRLLIYKF FRRLSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQVTQFPHTFGQGTRLEIK	CHIR-5.9 LCVR amino acid sequence
107	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIYPG DSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARGTAAGRDYYYYY GMDVWGQGTTVTVSSASTKGPSVFPLAPASKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGK	CHIR-5.9 heavy chain amino acid sequence
108	AIVMTQPPLSSPVTLGQPASISCRSSQSLVHSDGNTYLNWLQQRPGQPPRLLIYKF FRRLSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCMQVTQFPHTFGQGTRLEIK RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQES VTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	CHIR-5.9 light chain amino acid sequence
109	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYIN PSNDYTKYNQKFKDRATLTADKSANTAYMELSSLRSEDTAVYYCARQGFPYWGQ GTLVTVSS	Abiprubart [KPL-404], 2C10_h3 and 2C10HP HCVR amino acid sequence

110	YTFTNYWMH	Abiprubart [KPL-404] and 2C10 HCDR1 amino acid sequence
111	YINPSNDYTKYNQKFKD	Abiprubart [KPL-404] and 2C10 HCDR2 amino acid sequence
112	QGFPY	Abiprubart [KPL-404] and 2C10 HCDR3 amino acid sequence
113	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRRWIYDTSKLASG VPARFSGSGSGTDYTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIK	Abiprubart [KPL-404], 2C10_l2 and 2C10KP LCVR amino acid sequence
114	SASSSVSYMH	Abiprubart [KPL-404], and 2C10 LCDR1 amino acid sequence
115	DTSKLAS	Abiprubart [KPL-404] and 2C10 LCDR2 amino acid sequence
116	HQLSSDPFT	Abiprubart [KPL-404] and 2C10 LCDR3 amino acid sequence
117	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYIN PSNDYTKYNQKFKDRATLTADKSANTAYMELSSLRSEDTAVYYCARQGFPYWGQ GTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSG VHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPC PPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIS KAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSPG K	Abiprubart [KPL-404] heavy chain amino acid sequence
118	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRRWIYDTSKLASG VPARFSGSGSGTDYTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIKRTVAAPSV FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKD STYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Abiprubart [KPL-404] light chain amino acid sequence
119	QVKLQESGPGLVKPSETLSITCTVSGFSLSRYSVYWIRQPPGKGPEWMGMMWG GGSTDYSTSLKSRLTISKDTSKSQVSLKMNSLRTDDTAMYYCVRTDGDYWGQGTT VTVSS	PG102/FFP104 HCVR amino acid sequence
120	WGGGSTD	PG102/FFP104 HCDR2 amino acid sequence
121	ELQLTQSPLSLPVTLGQPASISCRSSQSLANSNGNTYLHWYLQRPGQSPRLLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGGGTKLEIKR	PG102/FFP104 LCVR amino acid sequence
122	RSSQSLANSNGNTYLH	PG102/FFP104 LCDR1 amino acid sequence
123	QVKLQESGPGLVKPSETLSITCTVSGFSLSRYSVYWIRQPPGKGPEWMGMMWG GGSTDYSTSLKSRLTISKDTSKSQVSLKMNSLRTDDTAMYYCVRTDGDYWGQGTT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPSC PAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	PG102/FFP104 heavy chain amino acid sequence

124	QVKLQESGPGLVKPSETLSITCTVSGFSLSRYSVYWIRQPPGKGPEWMGMMWG GGSTDYSTSLKSRLTISKDTSKSQVSLKMNSLRTDDTAMYYCVRTDGDYWGQGTT VTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHT FPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPPC PAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAK GQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	PG102/FFP104 heavy chain amino acid sequence
125	ELQLTQSPLSLPVTLGQPASISCRSSQSLANSNGNTYLHWYLQRPGQSPRLLIYKVS NRFSGVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCSQSTHVPWTFGGGTKLEIKR TVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESV TEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	PG102/FFP104 light chain amino acid sequence
126	EVQLVQSGAEVKKPGASVKVSCKASGYTFTTFPIEWVRQAPGQGLEWMGNFHP YNDDTKYNEKFKGRVTLTADKSTSTAYMELSRLRSEDTAVYYCARRGKLPFDSWG QGTTVTVSS	BIIB063 HCVR amino acid sequence
127	TFPIE	BIIB063 HCDR1 amino acid sequence
128	NFHPYNDDTKYNEKFKG	BIIB063 HCDR2 amino acid sequence
129	RGKLPFDS	BIIB063 HCDR3 amino acid sequence
130	DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKVPKLLIYFTSRLRSG VPSRFSGSGSGTDYTLTISSLQPEDVATYYCQQDRKLPWTFGQGTKLEIK	BIIB063 LCVR amino acid sequence
131	RASQDISNYLN	BIIB063 LCDR1 amino acid sequence
132	FTSRLRS	BIIB063 LCDR2 amino acid sequence
133	QQDRKLPWT	BIIB063 LCDR3 amino acid sequence
134	EVQLVQSGAEVKKPGASVKVSCKASGYTFTTFPIEWVRQAPGQGLEWMGNFHP YNDDTKYNEKFKGRVTLTADKSTSTAYMELSRLRSEDTAVYYCARRGKLPFDSWG QGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPP CPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTI SKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG	BIIB063 heavy chain amino acid sequence
135	DIQMTQSPSSLSASVGDRVTISCRASQDISNYLNWYQQKPGKVPKLLIYFTSRLRSG VPSRFSGSGSGTDYTLTISSLQPEDVATYYCQQDRKLPWTFGQGTKLEIKRTVAAP SVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDS KDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	BIIB063 light chain amino acid sequence
136	QVQLQESGGGLVQAGGSLRLSCAASGRTFGRSAMGWFRQAPGKEREFVAAIGT RGGSTKYADSVKGRFTISTDNASNTVYLQMDSLKPEDTAVYRCAVRGPGYPSAAIF QDEYHYWGQGTQVTVSS	V19 HCVR amino acid sequence
137	RSAMG	V19 HCDR1 amino acid sequence
138	AIGTRGGSTKYADSVKG	V19 HCDR2 amino acid sequence
139	RGPGYPSAAIFQDEYHY	V19 HCDR3 amino acid sequence

140	EVQLQESGGGLVQAGGSLRLSCVTSGSAFSSDTMGWFRQAPGKQRELVASISSR GVREYADSVKGRFTISRDNAKNTVYLQMNSLQPEDTAVYYCNRGALGLPGYRPY NNWGQGTQVTVSS	V15 HCVR amino acid sequence
141	SDTMG	V15 HCDR1 amino acid sequence
142	SISSRGVREYADSVKG	V15 HCDR2 amino acid sequence
143	GALGLPGYRPYNN	V15 HCDR3 amino acid sequence
144	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWMGYI NPSNDYTKYNQKFKDRVTITRDTSASTAYMELSSLRSEDTAVYYCARQGFPYWGQ GTLVTVSS	2C10_h1 HCVR amino acid sequence
145	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGI PARFSGSGSGTDFTLTISSLEPEDFAVYYCHQLSSDPFTFGGGTKVEIK	2C10_l1 LCVR amino acid sequence
146	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWMGYI NPSNDYTKYNQKFKDRVTITADKSASTAYMELSSLRSEDTAVYYCARQGFPYWGQ GTLVTVSS	2C10_h2 HCVR amino acid sequence
147	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYWMHWVRQAPGQRLEWIGYIN PSNDYTKYNQKFKDRATLTADTSTNTAYMELSSLRSEDTAVYYCARQGFPYWGQ GTLVTVSS	2C10HB1 HCVR amino acid sequence
148	DIQMTQSPSTLSASVGDRVTITCSASSSVSYMHWYQQKPGKAPKLLIYDTSKLASG VPARFSGSGSGTEFTLTISSLQPDDFATYYCHQLSSDPFTFGQGTKVEVK	2C10KB1 LCVR amino acid sequence
149	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTNYWMHWVRQAPGQGLEWIGYINP SNDYTKYNQKFKDKATITADESTNTAYMELSSLRSEDTAVYYCARQGFPYWGQGT LVTVSS	2C10HB2 HCVR amino acid sequence
150	EIVLTQSPATLSLSPGERATLSCSASSSVSYMHWYQQKPGQAPRLLIYDTSKLASGI PARFSGSGSGTDFTLTISSLEPEDFAVYYCHQLSSDPFTFGQGTKLEIK	2C10KB2 LCVR amino acid sequence
151	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMNWVRQAPGKGLEWIAYISSG RGNIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARSWGYFDVWGQ GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK THTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPI EKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGK	Ab101 heavy chain amino acid sequence
152	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYW AQGTLVTVSS	Antibody A HCVR amino acid sequence
153	DYGMH	Antibody A and Antibody B HCDR1 amino acid sequence
154	DIVMTQSPDSLAVSLGERATMSCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIY WTSTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVE IK	Antibody A LCVR amino acid sequence

155	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYW AQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	Antibody A heavy chain amino acid sequence
156	DIVMTQSPDSLAVSLGERATMSCKSSQSLLNSGNQKNYLTWHQQKPGQPPKLLIY WTSTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQNDYTYPLTFGGGTKVE IKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE SVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Antibody A light chain amino acid sequence
157	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYW AQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	Antibody A heavy chain amino acid sequence
158	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYW AQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEK TISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSL GK	Antibody A heavy chain amino acid sequence
159	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARQDGYRYAMDYW AQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK	Antibody A heavy chain amino acid sequence
160	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	Antibody B heavy chain amino acid sequence

161	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDY WGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPK SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPGK	Antibody B heavy chain amino acid sequence
162	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDYGMHWVRQAPGKGLEWVAYISSG NRIIYYADTVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQDGYRYAMDY WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPS SIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSL SLSLGK	Antibody B heavy chain amino acid sequence
163	QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDP EDGDSKYAPKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYW GQGTLVTVSS	Antibody C HCVR amino acid sequence
164	GFNIKDYYVH	Antibody C HCDR1 amino acid sequence
165	RIDPEDGDSKYAPKFQG	Antibody C HCDR2 amino acid sequence
166	SYYVGTYGY	Antibody C HCDR3 amino acid sequence
167	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMLWFQQKPGKAPKLLIYSTSNLASG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQRTFYPYTFGGGTKVEIK	Antibody C LCVR amino acid sequence
168	SASSSVSYML	Antibody C LCDR1 amino acid sequence
169	STSNLAS	Antibody C LCDR2 amino acid sequence
170	QQRTFYPYT	Antibody C LCDR3 amino acid sequence
171	QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDP EDGDSKYAPKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	Antibody C heavy chain amino acid sequence
172	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMLWFQQKPGKAPKLLIYSTSNLASG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQRTFYPYTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Antibody C light chain amino acid sequence

173	QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDP EDGDSKYAPKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQ PENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGK	Antibody C heavy chain amino acid sequence
174	QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDP EDGDSKYAPKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYW GQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYG PPCPPCPAPEFEGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIE KTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSL SLGK	Antibody C heavy chain amino acid sequence
175	QVQLVQSGAEVKKPGASVKVSCTASGFNIKDYYVHWVKQAPGQGLEWMGRIDP EDGDSKYAPKFQGKATMTADTSTSTVYMELSSLRSEDTAVYYCTTSYYVGTYGYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC DKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK	Antibody C heavy chain amino acid sequence
176	DIQLQQSGPGLVKPSQSLSLTCSVTGYSITTNYNWNWIRQFPGNKLEWMGYIRYD GTSEYTPSLKNRVSITRDTSMNQFFLRLTSVTPEDTATYYCARLDYWGQGTSVTVS S	G28.5 HCVR amino acid sequence
177	DAVMTQNPLSLPVSLGDEASISCRSSQSLENSNGNTFLNWFFQKPGQSPQLLIYRV SNRFSGVPDRFSGSGSGTDFTLKISRVEAEDLGVYFCLQVTHVPYTFGGGTTLEIK	G28.5 LCVR amino acid sequence
178	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQI NPTTGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAY WGQGTLVTVSS	Y12XX-hz28 [Vh-hzl4;Vk-hz2] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCVR amino acid sequence
179	SYWMH	Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCDR1 amino acid sequence
180	QINPTTGRSQYNEKFKT	Y12XX-hz28 [Vh-hzl4;Vk-hz2] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCDR2 amino acid sequence
181	WGLQPFAY	Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] HCDR3 amino acid sequence
182	DIQMTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYT GVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGTKVEIK	Y12XX-hz28 [Vh-hzl4;Vk-hz2] LCVR amino acid sequence

183	KASQDVSTAVA	Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCDR1 amino acid sequence
184	SASYRYT	Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCDR2 amino acid sequence
185	QQHYSTPWT	Y12XX-hz28 [Vh-hzl4;Vk-hz2], Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCDR3 amino acid sequence
186	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPTTGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	Y12XX-hz28 [Vh-hzl4;Vk-hz2] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] heavy chain amino acid sequence
187	DIQMTQSPSFLSASVGDRVTITCKASQDVSTAVAWYQQKPGKAPKLLIYSASYRYTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQHYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Y12XX-hz28 [Vh-hzl4;Vk-hz2] light chain amino acid sequence
188	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSQGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSS	Y12XX-hz40 [Vh-hzl2;Vk-hz3] HCVR amino acid sequence
189	QINPSQGRSQYNEKFKT	Y12XX-hz40 [Vh-hzl2;Vk-hz3] HCDR2 amino acid sequence
190	EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIK	Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] LCVR amino acid sequence
191	QVQLVQSGAEVKKPGSSVKVSCKASGYAFTSYWMHWVRQAPGQGLEWMGQINPSQGRSQYNEKFKTRVTITADKSTSTAYMELSSLRSEDTAVYYCARWGLQPFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGKSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG	Y12XX-hz40 [Vh-hzl2;Vk-hz3] heavy chain amino acid sequence
192	EIVMTQSPATLSVSPGERATLSCKASQDVSTAVAWYQQKPGQAPRLLIYSASYRYTGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQHYSTPWTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Y12XX-hz40 [Vh-hzl2;Vk-hz3] and Y12XX-hz42 [Vh-hzl4;Vk-hz3] light chain amino acid sequence

193	QVQLVQSGAEVVKPGASVKLSCKASGYIFTSYYMYWVKQAPGQGLEWIGEINPS NGDTNFNEKFKSKATLTVDKSASTAYMELSSLRSEDTAVYYCTRSDGRNDMDSW GQGTLVTVSS	Tegoprubart HCVR amino acid sequence
194	SYYMY	Tegoprubart HCDR1 amino acid sequence
195	EINPSNGDTNFNEKFKS	Tegoprubart HCDR2 amino acid sequence
196	SDGRNDMDS	Tegoprubart HCDR3 amino acid sequence
197	DIVLTQSPATLSVSPGERATISCRASQRVSSSTYSYMHWYQQKPGQPPKLLIKYAS NLESGVPARFSGSGSGTDFTLTISSVEPEDFATYYCQHSWEIPPTFGGGTKLEIK	Tegoprubart LCVR amino acid sequence
198	ISCRASQRVSSSTYSYMH	Tegoprubart LCDR1 amino acid sequence
199	YASNLES	Tegoprubart LCDR2 amino acid sequence
200	QHSWEIPPT	Tegoprubart LCDR3 amino acid sequence
201	QVQLVQSGAEVVKPGASVKLSCKASGYIFTSYYMYWVKQAPGQGLEWIGEINPS NGDTNFNEKFKSKATLTVDKSASTAYMELSSLRSEDTAVYYCTRSDGRNDMDSW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGAL TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSS DKTHTSPPSPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK	Tegoprubart heavy chain amino acid sequence
202	DIVLTQSPATLSVSPGERATISCRASQRVSSSTYSYMHWYQQKPGQPPKLLIKYAS NLESGVPARFSGSGSGTDFTLTISSVEPEDFATYYCQHSWEIPPTFGGGTKLEIKRTV AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTE QDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Tegoprubart light chain amino acid sequence
203	SQIEVKDVTDTTALITWSDDFGEYVWCELTYGIKDVPGDRTTIDLWYHHAHYSIGN LKPDTEYEVSLICRSGDMSSNPAKETFTTGGGGGGGGGGGGGGGRLDAPSQIEV KDVTDTTALITWSDDFGEYVWCELTYGIKDVPGDRTTIDLWYHHAHYSIGNLKPD TEYEVSLICRSGDMSSNPAKETFTTGGGGGGGGGGDAHKSEVAHRFKDLGEENF KALVLIAFAQYLQQSPFEDHVKLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCT VATLRETYGEMADCCAKQEPERNECFLQHKDDNPNLPRLVRPEVDVMCTAFHD NEETFLKKYLYEIARRHPYFYAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRD EGKASSAKQRLKCASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHT ECCHGDLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPA DLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLRLAKTYETTL EKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLGEYKFQNALLVRYTK KVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTP VSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQ TALVELVKHKPKATKEQLKAVMDDFAAFVEKCCKADDKETCFAEEGKKLVAASQA ALGL	Dazodalibep amino acid sequence

204	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGGCAGCTATGGCATGGCG TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGCTATTAGTG GTAGTGGTGATTATACAAACTACGCAGACTCCGTGAAGCGCCGGTTCACCATC TCCAGAGACAATTCCAAGAACACGCTTTATCTACAAATGAGCAGCCTGAGAGC CGAGGACACGGCCGTATATTACTGTGCGAAAGAGAAGACTGGAACGACGGGC TATTTGTACTCCGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTC CTCAGCCTCCACCAAGGGCCCATCGGTCTTCCCCCTGGCGCCCTGCTCCAGGAG CACCTCCGAGAGCACAGCCGCCCTGGGCTGCCTGGTCAAGGACTACTTCCCCG AACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACAC CTTCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGAC CGTGCCCTCCAGCAGCTTGGGCACGAAGACCTACACCTGCAACGTAGATCACA AGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGTCCAAATATGGTCCCCC ATGCCCACCGTGCCCAGCACCAGGCGGTGGCGGACCATCAGTCTTCCTGTTCC CCCCAAAACCCAAGGACACTCTCATGATCTCCCGGACCCCTGAGGTCACGTGC GTGGTGGTGGACGTGAGCCAGGAAGACCCCGAGGTCCAGTTCAACTGGTACG TGGATGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGT TCAACAGCACGTACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGG CTGAACGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGGCCTCCCGTCCTC CATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCCCCGAGAGCCACAGGTG TACACCCTGCCCCCATCCCAGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC CTGCCTGGTCAAAGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGC AATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCG ACGGCTCCTTCTTCCTCTACAGCAGGCTCACCGTGGACAAGAGCAGGTGGCAG GAGGGGAATGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTA CACACAGAAGTCCCTCTCCCTGTCTCTGGGTAAATGA	REGN20484 D1 heavy chain nucleic acid sequence
205	EVQLVESGGGLVQPGGSLRLSCAASGFTFGSYGMAWVRQAPGKGLEWVSAISGS GDYTNYADSVKRRFTISRDNSKNTLYLQMSSLRAEDTAVYYCAKEKTGTTGYLYSG MDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSW NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR VESKYGPPCPPCPAPGGGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK	REGN20484 D1 heavy chain amino acid sequence

206	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGCAGCTATGCCATGAAC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAATTATTAGTG GTACTATTGGTAAGACATACTACGCAGACTCCGTGAAGGGCCGGTTCACCATC TCTAGAGACAATTCCAAGAACACGCTCTATCTGCAAATGAACAGCCTGAGAGG CGAGGACACGGCCGTTTATTACTGTGCGAAAGATACGGAAAGGGATATAACT GGATCTCCTTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCCTCAGCC TCTACAAAGGGACCTTCTGTGTTTCCTCTGGCTCCTTGTTCTAGATCTACATCTG AATCTACAGCTGCTCTGGGATGTCTGGTGAAGGATTATTTTCCTGAACCTGTGA CAGTGTCTTGGAATTCTGGAGCTCTGACATCTGGAGTGCATACATTTCCTGCTG TGCTGCAGTCTTCTGGACTGTATTCTCTGTCTTCTGTGGTGACAGTGCCTTCTTC TTCTCTGGGAACAAAGACATATACATGTAATGTGGATCATAAGCCTTCTAATA CAAAGGTGGATAAGAGAGTGGAATCTAAGTATGGACCTCCTTGTCCTCCTTGT CCTGCTCCTGGCGGTGGCGGACCTTCTGTGTTTCTGTTTCCTCCTAAGCCTAAG GATACACTGATGATCTCTAGAACACCTGAAGTGACATGTGTGGTGGTGGATGT GTCTCAGGAAGATCCTGAAGTGCAGTTTAATTGGTATGTGGATGGAGTGGAA GTGCATAATGCTAAGACAAAGCCTAGAGAAGAACAGTTTAATTCTACATATAG AGTGGTGTCTGTGCTGACAGTGCTGCATCAGGATTGGCTGAATGGAAAGGAA TATAAGTGTAAGGTGTCTAATAAGGGACTGCCTTCTTCTATCGAAAAGACAATC TCTAAGGCTAAGGGACAGCCTAGAGAACCTCAGGTGTATACACTGCCTCCTTC TCAGGAAGAAATGACAAAGAATCAGGTGTCTCTGACATGTCTGGTGAAGGGA TTTTATCCTTCTGATATCGCTGTGGAATGGGAATCTAATGGACAGCCTGAAAAT AATTATAAGACAACACCTCCTGTGCTGGATTCTGATGGATCTTTTTTTCTGTATT CTAGACTGACAGTGGATAAGTCTAGATGGCAGGAAGGAAATGTGTTTTCTTGT TCTGTGATGCATGAAGCTCTGCATAATAGATTTACACAGAAGTCTCTGTCTCTG TCTCCTGGAAAGTAG	REGN20484 D2 heavy chain nucleic acid sequence
207	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSIISGTI GKTYYADSVKGRFTISRDNSKNTLYLQMNSLRGEDTAVYYCAKDTERDITGSPFDY WGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSG ALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESK YGPPCPPCPAPGGGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNW YVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSI EKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNRFTQKSLS LSPGK	REGN20484 D2 heavy chain amino acid sequence
1054	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCC CTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTAGTAACTTTTGGATGACC TGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTGGCCAACATGAAC CAAGATGGAAGTGAGAAATACTATGTGGACTCTGTGAAGGGCCGATTCACCAT CTCCAGAGACAACGCCAAGAGCTCACTGTATCTGCAAATGAACAGCCTGAGAG CCGAGGACACGGCTGTGTATTACTGTGCGAGAGATCGGGAATATTGTATTAGT ACCAGCTGCTATGATGACTTTGACTACTGGGGCCAGGGAACCCTGGTCACCGT CTCCTCA	Anti-BCMA HCVR DNA Sequence
1055	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFWMTWVRQAPGKGLEWVANMN QDGSEKYYVDSVKGRFTISRDNAKSSLYLQMNSLRAEDTAVYYCARDREYCISTSCY DDFDYWGQGTLVTVSS	Anti-BCMA HCVR Protein Sequence
1056	GGATTCACCTTTAGTAACTTTTGG	Anti-BCMA HCDR1 DNA Sequence
1057	GFTFSNFW	Anti-BCMA HCDR1 Protein Sequence
1058	ATGAACCAAGATGGAAGTGAGAAA	Anti-BCMA HCDR2 DNA Sequence

1059	MNQDGSEK	Anti-BCMA HCDR2 Protein Sequence
1060	GCGAGAGATCGGGAATATTGTATTAGTACCAGCTGCTATGATGACTTTGACTAC	Anti-BCMA HCDR3 DNA Sequence
1061	ARDREYCISTSCYDDFDY	Anti-BCMA HCDR3 Protein Sequence
1062	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCATAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA	Anti-BCMA LCVR DNA Sequence
1063	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLHSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK	Anti-BCMA LCVR Protein Sequence
1064	CAGAGCATTAGCAGCTAT	Anti-BCMA LCDR1 DNA Sequence
1065	QSISSY	Anti-BCMA LCDR1 Protein Sequence
1066	GCTGCATCC	Anti-BCMA LCDR2 DNA Sequence
1067	AAS	Anti-BCMA LCDR2 Protein Sequence
1068	CAACAGAGTTACAGTACCCCTCCGATCACC	Anti-BCMA LCDR3 DNA Sequence
1069	QQSYSTPPIT	Anti-BCMA LCDR3 Protein Sequence
1070	GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAAGCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCGTCAAGGTTCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCTCCGATCACCTTCGGCCAAGGGACACGACTGGAGATTAAA	Common LCVR DNA Sequence
1071	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK	Common LCVR Protein Sequence
1072	CAGAGCATTAGCAGCTAT	Common LCDR1 DNA Sequence
1073	QSISSY	Common LCDR1 Protein Sequence
1074	GCTGCATCC	Common LCDR2 DNA Sequence
1075	AAS	Common LCDR2 Protein Sequence
1076	CAACAGAGTTACAGTACCCCTCCGATCACC	Common LCDR3 DNA Sequence
1077	QQSYSTPPIT	Common LCDR3 Protein Sequence

1078	GAAGTACAGCTTGTAGAATCCGGCGGAGGACTGGTACAACCTGGAAGAAGTC TTAGACTGAGTTGCGCAGCTAGTGGGTTTACATTCGACGATTACAGCATGCAT TGGGTGAGGCAAGCTCCTGGTAAAGGATTGGAATGGGTTAGCGGGATATCAT GGAACTCAGGAAGCAAGGGATACGCCGACAGCGTGAAAGGCCGATTTACAAT ATCTAGGGACAACGCAAAAAACTCTCTCTACCTTCAAATGAACTCTCTTAGGGC AGAAGACACAGCATTGTATTATTGCGCAAAATACGGCAGTGGTTATGGCAAGT TTTATCATTATGGACTGGACGTGTGGGGACAAGGGACAACAGTGACAGTGAG TAGC	Anti-CD3 HCVR DNA Sequence – REGN5458
1079	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISW NSGSKGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYH YGLDVWGQGTTVTVSS	Anti-CD3 HCVR Protein Sequence – REGN5458
1080	GGGTTTACATTCGACGATTACAGC	Anti-CD3 HCDR1 DNA Sequence – REGN5458
1081	GFTFDDYS	Anti-CD3 HCDR1 Protein Sequence – REGN5458
1082	ATATCATGGAACTCAGGAAGCAAG	Anti-CD3 HCDR2 DNA Sequence – REGN5458
1083	ISWNSGSK	Anti-CD3 HCDR2 Protein Sequence – REGN5458
1084	GCAAAATACGGCAGTGGTTATGGCAAGTTTTATCATTATGGACTGGACGTG	Anti-CD3 HCDR3 DNA Sequence – REGN5458
1085	AKYGSGYGKFYHYGLDV	Anti-CD3 HCDR3 Protein Sequence – REGN5458
1086	GAAGTACAGCTTGTAGAATCCGGCGGAGGACTGGTACAACCTGGAAGAAGTC TTAGACTGAGTTGCGCAGCTAGTGGGTTTACATTCGACGATTACAGCATGCAT TGGGTGAGGCAAGCTCCTGGTAAAGGATTGGAATGGGTTAGCGGGATATCAT GGAACTCAGGAAGCATCGGATACGCCGACAGCGTGAAAGGCCGATTTACAAT ATCTAGGGACAACGCAAAAAACTCTCTCTACCTTCAAATGAACTCTCTTAGGGC AGAAGACACAGCATTGTATTATTGCGCAAAATACGGCAGTGGTTATGGCAAGT TTTATTATTATGGAATGGACGTGTGGGGACAAGGGACAACAGTGACAGTGAG TAGC	Anti-CD3 HCVR DNA Sequence – REGN5459
1087	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYYY GMDVWGQGTTVTVSS	Anti-CD3 HCVR Protein Sequence – REGN5459
1088	GGGTTTACATTCGACGATTACAGC	Anti-CD3 HCDR1 DNA Sequence – REGN5459
1089	GFTFDDYS	Anti-CD3 HCDR1 Protein Sequence – REGN5459
1090	ATATCATGGAACTCAGGAAGCATC	Anti-CD3 HCDR2 DNA Sequence – REGN5459
1091	ISWNSGSI	Anti-CD3 HCDR2 Protein Sequence – REGN5459
1092	GCAAAATACGGCAGTGGTTATGGCAAGTTTTATTATTATGGAATGGACGTG	Anti-CD3 HCDR3 DNA Sequence – REGN5459
1093	AKYGSGYGKFYYYGMDV	Anti-CD3 HCDR3 Protein Sequence – REGN5459

1094	EVQLVESGGGLVQPGGSLRLSCAASGFTFSNFWMTWVRQAPGKGLEWVANMN QDGSEKYYVDSVKGRFTISRDNAKSSLYLQMNSLRAEDTAVYYCARDREYCISTSCY DDFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYT QKSLSLSLGK	Anti-BCMA Heavy Chain Protein Sequence (IgG4 Heavy Chain Constant Region)
1095	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISW NSGSKGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYH YGLDVWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDK RVESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNRFT QKSLSLSPGK	Anti-CD3 Heavy Chain Protein Sequence (IgG4 Heavy Chain Constant Region with H435R/Y436F)
1096	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Common Anti-BCMA and Anti-CD3 Light Chain Protein Sequence (Kappa Light Chain Constant Region)
1097	EVQLVESGGGLVQPGRSLRLSCVASGFTFNDYAMHWVRQAPGKGLEWVSVISW NSDSIGYADSVKGRFTISRDNAKNSLYLQMHSLRAEDTALYYCAKDNHYGSGSYYY YQYGMDVWGQGTTVTVSS	Anti-CD20 HCVR Protein Sequence
1098	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRAT GIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQHYINWPLTFGGGTKVEIKR	Common LCVR Protein Sequence
1099	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYTMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKKSLYLQMNSLRAEDTALYYCAKDNSGYGHYYYG MDVWGQGTTVTVAS	Anti-CD3 HCVR Protein Sequence
1100	GFTFNDYA	Anti-CD20 HCDR1 Protein Sequence
1101	ISWNSDSI	Anti-CD20 HCDR2 Protein Sequence
1102	AKDNHYGSGSYYYYQYGMDV	Anti-CD20 HCDR3 Protein Sequence
1103	QSVSSN	Common LCDR1 Protein Sequence
1104	GAS	Common LCDR2 Protein Sequence
1105	QHYINWPLT	Common LCDR3 Protein Sequence
1106	GFTFDDYT	Anti-CD3 HCDR1 Protein Sequence
1107	ISWNSGSI	Anti-CD3 HCDR2 Protein Sequence
1108	AKDNSGYGHYYYGMDV	Anti-CD3 HCDR3 Protein Sequence
1109	CLPTRHMAC	CD40–CD40L blocking cyclic heptapetide
1110	HHHHHH	His-6
1111	HHHHHHHH	His-8

1112	HHHHHHHHHH	His-10
1114	HHHHHH	Hexahistidine
1115	aaaa

What is claimed is:

1. A method for inhibiting an immune response to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

2. The method of claim 1, wherein inhibiting the immune response comprises suppression of numbers and/or frequencies of immunogen-specific B cells.

3. The method of claim 1 or 2, wherein inhibiting the immune response comprises suppression of immunogen-specific IgG and/or IgM responses.

4. The method of any one of claims 1-3, wherein inhibiting the immune response comprises suppression of numbers and/or frequencies of follicular T helper cells (TFH) and/or CD4+ T cells.

5. The method of any one of claims 1-4, wherein inhibiting the immune response comprises suppression of immunogen-specific IFNγ responses.

6. The method of any one of claims 1-5, wherein inhibiting the immune response comprises suppression of magnitude and/or duration of the immune response.

7. A method for inhibiting generation of neutralizing antibodies to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

8. A method for preventing and/or suppressing an immunogen-specific T cell response in a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

9. The method of claim 8, wherein the prevention and/or suppression of the immunogen-specific T cell response comprises suppression of numbers and/or frequencies of the immunogen-specific T cells.

10. The method of claim 8 or 9, wherein the immunogen-specific T cells comprise follicular T helper cells (TFH) and/or CD4+ T cells.

11. The method of any one of claims 8-10, wherein the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or a tissue in the subject in response to the immunogen.

12. The method of any one of claims 8-11, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle, and the prevention and/or suppression of the immunogen-specific T cell response comprises increasing or maintaining the level of transgene expression in the subject.

13. The method of claim 12, wherein the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or tissue in the subject in response to transgene expression in the organ and/or a tissue.

14. The method of any one of claims 11-13, wherein the tissue is muscle.

15. The method of any one of claims 11-13, wherein the organ is liver.

16. A method for increasing effectiveness of re-administration of an immunogen to a subject in need thereof, comprising administering to the subject an effective amount of a CD40 inhibitor.

17. The method of claim 16, wherein the immunogen re-administration occurs via the same administration route as its prior administration.

18. The method of claim 16, wherein the immunogen re-administration occurs via a different administration route than its prior administration.

19. The method of any one of claims 1-18, wherein the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

20. The method of any one of claims 1-18, wherein the method comprises determining the level of non-neutralizing antibodies in the subject.

21. The method of any one of claims 1-20, wherein the CD40 inhibitor is administered before the administration of the immunogen to the subject.

22. The method of any one of claims 1-20, wherein the CD40 inhibitor is administered simultaneously with the administration of the immunogen to the subject.

23. The method of any one of claims 1-20, wherein the CD40 inhibitor is administered after the administration of the immunogen to the subject.

24. The method of any one of claims 1-20, wherein the immunogen is administered to the subject two or more times and the CD40 inhibitor is administered before and/or between each of the administrations of the immunogen.

25. The method of any one of claims 1-24, wherein the subject has a preexisting immune response to the immunogen.

26. The method of any one of claims 1-24, further comprising administering to the subject an immunoglobulin depleting agent.

27. The method of claim 26, wherein the immunoglobulin depleting agent is administered before the administration of the CD40 inhibitor to the subject, and the CD40 inhibitor is administered before the administration of the immunogen to the subject.

28. The method of claim 26, wherein the CD40 inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, and the immunoglobulin depleting agent is administered before the administration of the immunogen to the subject.

29. The method of any one of claims 26-28, wherein the CD40 inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject has preexisting immunity against the immunogen.

30. The method of any one of claims 26-28, wherein the CD40 inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject does not have preexisting immunity against the immunogen.

31. The method of any one of claims 26-30, wherein the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40 inhibitor is resistant to said immunoglobulin degrading enzyme.

32. The method of claim 31, wherein the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, and HNSA-5487.

33. The method of claim 32, wherein the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

34. The method of any one of claims 1-33, further comprising administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogen.

35. The method of claim 34, wherein the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

36. The method of claim 34 or 35, wherein the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

37. The method of claim 36, wherein the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

38. The method of claim 37, wherein the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from

linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

39. The method of claim 38, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

40. The method of claim 39, wherein the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

41. The method of claim 39 or 40, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

42. The method of claim 41, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

43. The method of any one of claims 39-42, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:
(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and
(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

44. The method of any one of claims 39-42, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:
(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and
(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

45. The method of any one of claims 38-44, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

46. The method of claim 45, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

47. The method of claim 45, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

48. The method of any one of claims 34-47, further comprising administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogen.

49. The method of claim 48, wherein the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

50. The method of claim 48 or 49, wherein the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

51. The method of any one of claims 48-50, wherein the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

52. The method of any one of claims 48-51, wherein the B cell depleting agent is an agent that binds to a B cell surface molecule.

53. The method of claim 52, wherein the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

54. The method of claim 53, wherein the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

55. The method of any one of claims 48-53, wherein the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

56. The method of claim 55, wherein the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

57. The method of claim 56, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

58. The method of claim 57, wherein the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

59. The method of claim 57 or 58, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

60. The method of claim 59, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

61. The method of any one of claims 57-60, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

62. The method of any one of claims 56-61, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

63. The method of claim 62, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

64. The method of claim 62, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

65. The method of any one of claims 48-51, wherein the B cell depleting agent is an agent targeting a B cell survival factor.

66. The method of any one of claims 48-51, wherein the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

67. The method of any one of claims 48-66, wherein the immunoglobulin depleting agent is capable of accelerating IgG clearance.

68. The method of any one of claims 48-67, wherein the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

69. The method of claim 68, wherein the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

70. The method of any one of claims 34-69, wherein the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

71. The method of any one of claims 34-70, wherein the plasma cell depleting agent is administered simultaneously with the immunogen, prior to the immunogen, or prior to and after the immunogen,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogen and the plasma cell depleting agent is administered if the immunogen is still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogen.

72. The method of any one of claims 34-71, wherein the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent is administered prior to the CD40 inhibitor.

73. The method of any one of claims 34-71, wherein the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent and the CD40 inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogen when the plasma cell depleting agent and the CD40 inhibitor are administered.

74. The method of any one of claims 34-71, wherein:

(I) the subject does not have preexisting immunity against the immunogen before administration of a first dose of the immunogen, the CD40 inhibitor is administered prior to the first dose of the immunogen, the subject develops immunity against the immunogen from the first dose of the immunogen, and the plasma cell depleting agent is administered after the first dose of the immunogen but prior to a second dose of the immunogen; or

(II) the subject does not have preexisting immunity against the immunogen before administration of the immunogen, the CD40 inhibitor is administered prior to the immunogen, the subject develops immunity against the immunogen from the administration of the immunogen, and the plasma cell depleting agent is administered after the immunogen but prior to administration of a second immunogen.

75. The method of any one of claims 1-74, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

76. The method of claim 75, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

77. The method of claim 75, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

78. The method of any one of claims 1-74, wherein the immunogen is an immunoglobulin depleting agent.

79. The method of claim 78, wherein the immunoglobulin depleting agent is administered before the administration of the CD40 inhibitor to the subject at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

80. The method of claim 78, wherein the immunoglobulin depleting agent is administered before the administration of the CD40 inhibitor to the subject at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

81. The method of claim 78, wherein the CD40 inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

82. The method of claim 78, wherein the CD40 inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

83. The method of any one of claims 78-82, wherein the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40 inhibitor is resistant to said immunoglobulin degrading enzyme.

84. The method of claim 83, wherein the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, HNSA-5487 .

85. The method of claim 84, wherein the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

86. A method for increasing or maintaining the level of a transgene expression in a subject in need thereof, said method comprising administering to the subject an effective amount of a CD40 inhibitor.

87. The method of claim 86, wherein the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

88. The method of claim 86, wherein the method comprises determining the level of non-neutralizing antibodies in the subject.

89. The method of any one of claims 86-88, wherein the transgene is delivered to the subject via an immunogenic delivery vehicle.

90. The method of any one of claims 86-89, wherein the level of transgene expression is increased or maintained by inhibiting an immune response to the immunogenic delivery vehicle and/or by inhibiting an immune response to the transgene product(s).

91. The method of claim 90, wherein the level of transgene expression is increased or maintained by inhibiting antibody responses to the transgene product(s).

92. The method of any one of claims 86-91, wherein the CD40 inhibitor is administered before the administration of the immunogenic delivery vehicle to the subject.

93. The method of any one of claims 86-91, wherein the CD40 inhibitor is administered simultaneously with the administration of the immunogenic delivery vehicle to the subject.

94. The method of any one of claims 86-91, wherein the CD40 inhibitor is administered after the administration of the immunogenic delivery vehicle to the subject.

95. The method of any one of claims 86-91, wherein the immunogenic delivery vehicle is administered to the subject two or more times and the CD40 inhibitor is administered before and/or between each of the administrations of the immunogenic delivery vehicle.

96. The method of any one of claims 86-95, wherein the subject has a preexisting immune response to the immunogenic delivery vehicle and/or to the transgene product(s).

97. The method of any one of claims 86-96, further comprising administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

98. The method of claim 97, wherein the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

99. The method of claim 97 or 98, wherein the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

100. The method of claim 99, wherein the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

101. The method of claim 100, wherein the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

102. The method of claim 101, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

103. The method of claim 102, wherein the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057,

a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

104. The method of claim 102 or 103, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

105. The method of claim 104, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

106. The method of any one of claims 102-105, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

107. The method of any one of claims 102-105, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

108. The method of any one of claims 101-107, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

109. The method of claim 108, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

110. The method of claim 108, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

111. The method of any one of claims 97-110, further comprising administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

112. The method of claim 111, wherein the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

113. The method of claim 111 or 112, wherein the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

114. The method of any one of claims 111-113, wherein the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

115. The method of any one of claims 111-114, wherein the B cell depleting agent is an agent that binds to a B cell surface molecule.

116. The method of claim 115, wherein the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

117. The method of claim 116, wherein the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

118. The method of any one of claims 111-116, wherein the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

119. The method of claim 118, wherein the multispecific anti-CD20 antibody or functional fragment thereof is anti-CD20xCD3 bispecific antibody or functional fragment thereof.

120. The method of claim 119, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

121. The method of claim 120, wherein the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising

the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

122. The method of claim 120 or 121, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

123. The method of claim 122, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

124. The method of any one of claims 120-123, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

125. The method of any one of claims 119-124, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant

region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

126. The method of claim 125, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

127. The method of claim 125, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

128. The method of any one of claims 111-114, wherein the B cell depleting agent is an agent targeting a B cell survival factor.

129. The method of any one of claims 111-114, wherein the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

130. The method of any one of claims 111-129, wherein the immunoglobulin depleting agent is capable of accelerating IgG clearance.

131. The method of any one of claims 111-130, wherein the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

132. The method of claim 131, wherein the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

133. The method of any one of claims 97-132, wherein the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

134. The method of any one of claims 97-133, wherein the plasma cell depleting agent is administered simultaneously with the immunogenic delivery vehicle, prior to the immunogenic delivery vehicle, or prior to and after the immunogenic delivery vehicle,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogenic delivery vehicle and the plasma cell depleting agent is administered if the immunogenic delivery vehicle and/or transgene product(s) are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogenic delivery vehicle.

135. The method of any one of claims 97-134, wherein the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent is administered prior to the CD40 inhibitor.

136. The method of any one of claims 97-134, wherein the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent and the CD40 inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogenic delivery vehicle and/or to the transgene product(s) when the plasma cell depleting agent and the CD40 inhibitor are administered.

137. The method of any one of claims 97-134, wherein:

(I) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of a first dose of the immunogenic delivery vehicle, the CD40 inhibitor is administered prior to the first dose of the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene product(s) from the first dose of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the first dose of the immunogenic delivery vehicle but prior to administration of a second dose of the immunogenic delivery vehicle; or

(II) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of the immunogenic delivery vehicle, the CD40 inhibitor is administered prior to the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene

product(s) from the administration of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the immunogenic delivery vehicle but prior to administration of a second immunogenic delivery vehicle.

138. The method of any one of claims 89-137, wherein the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

139. The method of claim 138, wherein the immunogenic delivery vehicle is a viral vector.

140. A method for increasing effectiveness of administration of a subsequently administered viral vector following administration of an originally administered viral vector in a subject in need thereof, said method comprising administering to the subject an effective amount of a CD40 inhibitor, wherein the subsequently administered viral vector is of the same or similar viral origin as the originally administered viral vector.

141. The method of claim 140, wherein the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

142. The method of claim 140, wherein the method comprises determining the level of non-neutralizing antibodies in the subject.

143. The method of any one of claims 140-142, wherein the subsequently administered viral vector is administered via the same administration route as the originally administered viral vector.

144. The method of any one of claims 140-142, wherein the subsequently administered viral vector is administered via a different administration route from the originally administered viral vector.

145. The method of any one of claims 140-144, wherein the CD40 inhibitor is administered before the administration of the originally administered viral vector to the subject.

146. The method of any one of claims 140-144, wherein the CD40 inhibitor is administered simultaneously with the administration of the originally administered viral vector and/or subsequently administered viral vector to the subject.

147. The method of any one of claims 140-144, wherein the CD40 inhibitor is administered after the administration of the originally administered viral vector but before administering the subsequently administered viral vector to the subject.

148. The method of any one of claims 140-144, wherein the CD40 inhibitor is administered after the administration of the subsequently administered viral vector to the subject.

149. The method of any one of claims 140-144, wherein the CD40 inhibitor is administered before and/or between each of the subsequently administered administrations of the viral vectors to the subject.

150. The method of any one of claims 140-149, wherein the subject has a preexisting immune response to the viral vectors.

151. The method of any one of claims 140-150, further comprising administering to the subject a plasma cell depleting agent when the subject has preexisting immunity against the viral vectors.

152. The method of claim 151, wherein the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

153. The method of claim 151 or 152, wherein the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

154. The method of claim 153, wherein the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

155. The method of claim 154, wherein the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

156. The method of claim 155, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

157. The method of claim 156, wherein the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

158. The method of claim 156 or 157, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

159. The method of claim 158, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a

LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

160. The method of any one of claims 156-159, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

161. The method of any one of claims 156-159, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

162. The method of any one of claims 155-161, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

163. The method of claim 162, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

164. The method of claim 162, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

165. The method of any one of claims 151-164, further comprising administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent when the subject has preexisting immunity against the viral vectors.

166. The method of claim 165, wherein the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

167. The method of claim 165 or 166, wherein the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

168. The method of any one of claims 165-167, wherein the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

169. The method of any one of claims 165-168, wherein the B cell depleting agent is an agent that binds to a B cell surface molecule.

170. The method of claim 169, wherein the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

171. The method of claim 170, wherein the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

172. The method of any one of claims 165-170, wherein the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a

multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

173. The method of claim 172, wherein the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

174. The method of claim 173, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

175. The method of claim 174, wherein the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

176. The method of claim 174 or 175, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

177. The method of claim 176, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of

SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

178. The method of any one of claims 174-177, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

179. The method of any one of claims 173-178, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

180. The method of claim 179, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

181. The method of claim 179, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

182. The method of any one of claims 165-168, wherein the B cell depleting agent is an agent targeting a B cell survival factor.

183. The method of any one of claims 165-168, wherein the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

184. The method of any one of claims 165-183, wherein the immunoglobulin depleting agent is capable of accelerating IgG clearance.

185. The method of any one of claims 165-184, wherein the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

186. The method of claim 185, wherein the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

187. The method of any one of claims 151-186, wherein the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

188. The method of any one of claims 151-187, wherein the plasma cell depleting agent is administered simultaneously with the viral vectors, prior to the viral vectors, or prior to and after the viral vectors,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the viral vectors and the plasma cell depleting agent is administered if the viral vectors are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior the viral vectors.

189. The method of any one of claims 151-188, wherein the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent is administered prior to the CD40 inhibitor.

190. The method of any one of claims 151-188, wherein the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40 inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent and the CD40 inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the viral vectors when the plasma cell depleting agent and the CD40 inhibitor are administered.

191. The method of any one of claims 151-188, wherein:

(I) the subject does not have preexisting immunity against the viral vectors before administration of a first dose of the viral vectors, the CD40 inhibitor is administered prior to the first dose of the viral vectors, the subject develops immunity against the viral vectors from the first dose of the viral vectors, and the plasma cell depleting agent is administered after the first dose of the viral vectors but prior to a second dose of the viral vectors; or

(II) the subject does not have preexisting immunity against the viral vectors before administration of the viral vectors, the CD40 inhibitor is administered prior to the viral vectors, the subject develops immunity against the viral vectors from the administration of the viral vectors, and the plasma cell depleting agent is administered after the viral vectors but prior to administration of second viral vectors.

192. The method of any one of claims 140-191, wherein the viral vectors are derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

193. The method of claim 192, wherein the viral vectors are derived from AAV.

194. The method of claim 193, wherein the subsequently administered AAV vector has a capsid derived from the same AAV serotype as the originally administered AAV vector.

195. The method of claim 192, wherein the retrovirus is a lentivirus.

196. The method of any one of claims 140-191, wherein the viral vectors are derived from an oncolytic virus.

197. The method of claim 196, wherein the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

198. The method of any one of claims 1-197, wherein the CD40 inhibitor

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

199. The method of any one of claims 1-198, wherein the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

200. The method of claim 199, wherein the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof.

201. The method of claim 199 or 200, wherein the anti-CD40 antibody is an anti-CD40 monospecific antibody or a functional fragment thereof.

202. The method of any one of claims 199-201, wherein the anti-CD40 antibody is an anti-CD40 bivalent antibody or a functional fragment thereof.

203. The method of any one of claims 199-201, wherein the anti-CD40 antibody is an anti-CD40 biparatopic antibody or a functional fragment thereof.

204. The method of claim 199 or 200, wherein the anti-CD40 antibody is a multispecific antibody or a functional fragment thereof.

205. The method of claim 199 or 200, wherein the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

206. The method of any one of claims 199-205, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain variable region (HCVR) comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77,

86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188, or a variant thereof; and/or

b) a light chain variable region (LCVR) comprising the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence of SEQ ID NO: 10, 61, 71, 81, 90, 100, 106, 113, 121, 130, 145, 148, 150, 154, 167, 177, 182 or 190, or a variant thereof.

207. The method of any one of claims 199-206, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR comprising

the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

208. The method of any one of claims 199-207, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR

comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

209. The method any one of claims 199-208, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

d) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 58, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof;

e) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 68, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

f)an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 78, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

g) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 87, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

92, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93, or a variant thereof;

h) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

i) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 110, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof;

j) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

k) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 127, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof;

l) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 153, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

m) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 164, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof;

n) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof; and/or

o) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof.

210. The method of any of claims 199-209, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and/or

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

211. The method of any one of claims 199-210, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t)an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

212. The method of any one of claims 199-211, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

213. The method of any one of claims 199-212, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

d) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 65, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

e) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 75, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

f) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 84, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

g) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 94, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 95, or a variant thereof;

h) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 104, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

i) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 107, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 108, or a variant thereof;

j) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 117, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 118, or a variant thereof;

k) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 123, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

l) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

m) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 134, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 135, or a variant thereof;

n) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 151, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

o) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 155, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

p) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 157, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

q) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 158, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

r) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 159, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

s) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 160, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

t) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 161, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

u) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 162, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

v) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 171, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

w) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 173, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

x) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 174, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

y) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 175, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

z) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 187, or a variant thereof;

aa) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 191, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof; and/or

bb) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof.

214. The method of any one of claims 199-213, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and/or

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

215. The method of claim 205, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

216. The method of claim 215, wherein the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or variant thereof; and

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or variant thereof.

217. The method of claim 215 or 216, wherein the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein

the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, or a variant thereof, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16, or a variant thereof,.

218. The method of any one of claims 215-217, wherein the D1 domain comprises:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

219. The method of claim 218, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the

amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

220. The method of claim 219, wherein the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

221. The method of claim 218, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

222. The method of claim 221, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof.

223. The method of claim 218, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

224. The method of claim 223, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

225. The method of any one of claims 215-224, wherein the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

226. The method of any one of claims 215-225, wherein the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3

comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

227. The method of claim 226, wherein the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

228. The method of any one of claims 215-225, wherein the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

229. The method of claim 228, wherein the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

230. The method of any one of claims 226-229, wherein the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

231. The method of any one of claims 215-220, 225-227, and 230, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and
a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO:

12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

232. The method of claim 231, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

233. The method of any one of claims 215-218, 221-222, 225-227, and 230, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and
a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

234. The method of claim 233, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

235. The method of any one of claims 215-218, 223-225, and 228-230, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and
a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

236. The method of claim 235, wherein the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

237. The method of any one of claims 200-236, wherein the anti-CD40 antibody or the functional fragment thereof comprises a human IgG heavy chain constant region.

238. The method of claim 237, wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

239. The method of claim 238, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

240. The method of claim 238, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

241. The method of any one of claims 215-240, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D1 domain comprising:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

242. The method of any one of claims 215-241, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a D2 domain comprising:

a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or

a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

243. The method of any one of claims 215-242, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of

SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

244. The method of any one of claims 215-242, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

245. The method of any one of claims 215-242, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

246. The method of any one of claims 215-242, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

247. The method of any one of claims 215-242, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

248. A composition comprising an immunogen and a CD40 inhibitor and optionally further comprising a pharmaceutically acceptable carrier and/or excipient.

249. The composition of claim 248, wherein the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

250. The composition of claim 249, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

251. The composition of claim 249, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

252. The composition of claim 249, wherein the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

253. The composition of claim 252, wherein the immunogenic delivery vehicle is a viral vector.

254. The composition of claim 253, wherein the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

255. The composition of claim 254, wherein the viral vector is derived from AAV.

256. The composition of claim 254, wherein the retrovirus is a lentivirus.

257. The composition of claim 253, wherein the viral vector is derived from an oncolytic virus.

258. The composition of claim 257, wherein the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

259. The composition of any one of claims 248-258, wherein the CD40 inhibitor:

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

260. The composition of any one of claims 248-259, wherein the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

261. The composition of claim 260, wherein the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof.

262. The composition of claim 260 or 261, wherein the anti-CD40 antibody is an anti-CD40 monospecific antibody or a functional fragment thereof.

263. The composition of any one of claims 260-262, wherein the anti-CD40 antibody is an anti-CD40 bivalent antibody or a functional fragment thereof.

264. The composition of any one of claims 260-262, wherein the anti-CD40 antibody is an anti-CD40 biparatopic antibody or a functional fragment thereof.

265. The composition of claim 260 or 261, wherein the anti-CD40 antibody is a multispecific antibody or a functional fragment thereof.

266. The composition of claim 260 or 261, wherein the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

267. The composition of any one of claims 260-266, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain variable region (HCVR) comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188, or a variant thereof; and/or

b) a light chain variable region (LCVR) comprising the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence of SEQ ID NO: 10, 61, 71, 81, 90, 100, 106, 113, 121, 130, 145, 148, 150, 154, 167, 177, 182 or 190, or a variant thereof.

268. The composition of any one of claims 260-267, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f)an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR comprising

the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t) anHCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

269. The composition of any one of claims 260-268, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

270. The composition of any one of claims 260-269, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

d) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 58, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof;

e) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 68, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

f) anHCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 78, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

g) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 87, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88,

or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 92, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93, or a variant thereof;

h) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

i) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 110, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof;

j) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

k) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 127, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof;

l) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 153, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

m) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 164, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof;

n) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof; and/or

o) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof.

271. The composition of any one of claims 260-270, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and/or

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

272. The composition of any one of claims 260-271, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

273. The composition of any one of claims 260-272, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

274. The composition of any one of claims 260-273, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

d) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 65, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

e) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 75, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

f) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 84, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

g) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 94, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 95, or a variant thereof;

h) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 104, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

i) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 107, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 108, or a variant thereof;

j) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 117, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 118, or a variant thereof;

k) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 123, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

l) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

m) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 134, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 135, or a variant thereof;

n) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 151, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

o) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 155, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

p) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 157, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

q) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 158, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

r) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 159, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

s) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 160, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

t) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 161, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

u) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 162, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

v) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 171, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

w) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 173, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

x) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 174, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

y) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 175, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

z) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 187, or a variant thereof;

aa) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 191, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof; and/or

bb) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof.

275. The composition of any one of claims 260-274, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and/or

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

276. The composition of claim 266, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

277. The composition of claim 276, wherein the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof.

278. The composition of claim 276 or 277, wherein the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, or a variant thereof, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

279. The composition of any one of claims 276-278, wherein the D1 domain comprises:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26 or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36 or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

280. The composition of claim 279, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the

amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

281. The composition of claim 280, wherein the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

282. The composition of claim 279, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

283. The composition of claim 282, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof.

284. The composition of claim 279, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

285. The composition of claim 284, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

286. The composition of any one of claims 276-285, wherein the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

287. The composition of any one of claims 276-286, wherein the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

288. The composition of claim 287, wherein the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

289. The composition of any one of claims 276-286, wherein the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

290. The composition of claim 289, wherein the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

291. The composition of any one of claims 287-290, wherein the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

292. The composition of any one of claims 276-281, 286-288, and 291, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

293. The composition of claim 292, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

294. The composition of any one of claims 276-279, 282-283, 286-288, and 291, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and
a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

295. The composition of claim 294, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

296. The composition of any one of claims 276-279, 284-286, 289-291, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and
a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

297. The composition of claim 296, wherein the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

298. The composition of any one of claims 261-297, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a human IgG heavy chain constant region.

299. The composition of claim 298, wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

300. The composition of claim 299, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

301. The composition of claim 299, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

302. The composition of any one of claims 276-301, wherein the D1 domain comprises:
a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

303. The composition of any one of claims 276-302, wherein the D2 domain comprises:
a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

304. The composition of any one of claims 276-303, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

305. The composition of any one of claims 276-303, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

306. The composition of any one of claims 276-303, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

307. The composition of any one of claims 276-303, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

308. The composition of any one of claims 276-303, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

309. A kit comprising (i) an immunogen, (ii) a CD40 inhibitor, and (iii) optionally, instructions for use.

310. The kit of claim 309, wherein the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

311. The kit of claim 310, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

312. The kit of claim 310, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

313. The kit of claim 310, wherein the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

314. The kit of claim 313, wherein the immunogenic delivery vehicle is a viral vector.

315. The kit of claim 314, wherein the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

316. The kit of claim 315, wherein the viral vector is derived from AAV.

317. The kit of claim 315, wherein the retrovirus is a lentivirus.

318. The kit of claim 314, wherein the viral vector is derived from an oncolytic virus.

319. The kit of claim 318, wherein the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

320. The kit of any one of claims 309-319, wherein the CD40 inhibitor:

(i) binds human CD40 with a K_D of less than 25 nM as measured by surface plasmon resonance at 25°C;

(ii) binds human CD40 with a K_D of less than 70 nM as measured by surface plasmon resonance at 37°C;

(iii) binds human CD40 with a dissociative half-life ($t_{1/2}$) of greater than 75 minutes as measured by surface plasmon resonance at 25°C;

(iv) binds a human CD40-expressing cell with an EC_{50} value of about 10 nM or less;

(v) inhibits binding of human CD40 monomer to CD40L;

(vi) inhibits CD40 ligand (CD40L)-induced activation; and/or

(vii) does not significantly agonize CD40 in the absence of CD40L.

321. The kit of any one of claims 309-320, wherein the CD40 inhibitor is an anti-CD40 antibody or a functional fragment thereof.

322. The kit of claim 321, wherein the anti-CD40 antibody is an antagonistic anti-CD40 antibody or a functional fragment thereof.

323. The kit of claim 321 or 322, wherein the anti-CD40 antibody is a monospecific anti-CD40 antibody or the functional fragment thereof.

324. The kit of any one of claims 321-323, wherein the anti-CD40 antibody is an anti-CD40 bivalent antibody or a functional fragment thereof.

325. The kit of any one of claims 321-323, wherein the anti-CD40 antibody is an anti-CD40 biparatopic antibody or a functional fragment thereof.

326. The kit of claim 321 or 322, wherein the anti-CD40 antibody is a multispecific anti-CD40 antibody or the functional fragment thereof.

327. The kit of claim 321 or 322, wherein the anti-CD40 antibody is an anti-CD40xCD40 bispecific antibody or a functional fragment thereof, wherein both antigen-binding domains bind to CD40.

328. The kit of any one of claims 321-327, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain variable region (HCVR) comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, 22, 32, 57, 67, 77, 86, 96, 105, 109, 119, 126, 136, 140, 144, 146, 147, 149, 152, 163, 176, 178, or 188, or a variant thereof; and/or

b) a light chain variable region (LCVR) comprising the LCDR1, LCDR2 and LCDR3 of a LCVR that comprises the amino acid sequence of SEQ ID NO: 10, 61, 71, 81, 90, 100, 106, 113, 121, 130, 145, 148, 150, 154, 167, 177, 182 or 190, or a variant thereof.

329. The kit of claim 321-328, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR comprising

the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR

comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

330. The kit of any one of claims 321-329, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

331. The kit of any one of claims 321-330, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26,

or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

d) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 58, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 59, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 60, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 62, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 63, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 64, or a variant thereof;

e) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 68, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 69, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 70, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 72, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 73, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

f) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 78, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

g) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 87, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 91, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 92, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 93, or a variant thereof;

h) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 98, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 101, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

i) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 110, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 111, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 112, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 114, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 116, or a variant thereof;

j) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 97, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 99, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 122, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

102, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof;

k) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 127, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 128, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 129, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 133, or a variant thereof;

l) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 153, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 79, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 80, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 82, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 83, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 74, or a variant thereof;

m) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 164, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 165, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 166, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof;

n) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 180, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof; and/or

o) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 179, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 181, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 184, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 185, or a variant thereof.

332. The kit of any one of claims 321-331, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof;

b) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and/or

c) an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO:

14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

333. The kit of any one of claims 321-332, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

d) an HCVR that comprises the amino acid sequence of SEQ ID NO: 57, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 61, or a variant thereof;

e) an HCVR that comprises the amino acid sequence of SEQ ID NO: 67, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 71, or a variant thereof;

f) an HCVR that comprises the amino acid sequence of SEQ ID NO: 77, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 81, or a variant thereof;

g) an HCVR that comprises the amino acid sequence of SEQ ID NO: 86, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 90, or a variant thereof;

h) an HCVR that comprises the amino acid sequence of SEQ ID NO: 96, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 100, or a variant thereof;

i) an HCVR that comprises the amino acid sequence of SEQ ID NO: 105, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 106, or a variant thereof;

j) an HCVR that comprises the amino acid sequence of SEQ ID NO: 109, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 113, or a variant thereof;

k) an HCVR that comprises the amino acid sequence of SEQ ID NO: 119, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 121, or a variant thereof;

l) an HCVR that comprises the amino acid sequence of SEQ ID NO: 126, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 130, or a variant thereof;

m) an HCVR that comprises the amino acid sequence of SEQ ID NO: 144, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

n) an HCVR that comprises the amino acid sequence of SEQ ID NO: 146, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 145, or a variant thereof;

o) an HCVR that comprises the amino acid sequence of SEQ ID NO: 147, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 148, or a variant thereof;

p) an HCVR that comprises the amino acid sequence of SEQ ID NO: 149, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 150, or a variant thereof;

q) an HCVR that comprises the amino acid sequence of SEQ ID NO: 152, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 154, or a variant thereof;

r) an HCVR that comprises the amino acid sequence of SEQ ID NO: 163, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 167, or a variant thereof;

s) an HCVR that comprises the amino acid sequence of SEQ ID NO: 176, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 177, or a variant thereof;

t) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 182, or a variant thereof;

u) an HCVR that comprises the amino acid sequence of SEQ ID NO: 188, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof; and/or

v) an HCVR that comprises the amino acid sequence of SEQ ID NO: 178, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 190, or a variant thereof.

334. The kit of any one of claims 321-333, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) an HCVR that comprises the amino acid sequence of SEQ ID NO: 2, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof;

b) an HCVR that comprises the amino acid sequence of SEQ ID NO: 22, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof; and/or

c) an HCVR that comprises the amino acid sequence of SEQ ID NO: 32, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

335. The kit of any one of claims 321-334, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

d) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 65, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

e) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 75, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

f) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 84, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

g) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 94, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 95, or a variant thereof;

h) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 104, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 66, or a variant thereof;

i) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 107, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 108, or a variant thereof;

j) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 117, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 118, or a variant thereof;

k) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 123, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

l) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 124, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 125, or a variant thereof;

m) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 134, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 135, or a variant thereof;

n) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 151, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 76, or a variant thereof;

o) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 155, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

p) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 157, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

q) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 158, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

r) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 159, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 156, or a variant thereof;

s) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 160, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

t) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 161, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

u) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 162, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 85, or a variant thereof;

v) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 171, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

w) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 173, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

x) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 174, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

y) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 175, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 172, or a variant thereof;

z) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 187, or a variant thereof;

aa) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 191, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof; and/or

bb) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 186, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 192, or a variant thereof.

336. The kit of any one of claims 321-335, wherein the anti-CD40 antibody or the functional fragment thereof comprises:

a) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 18, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof;

b) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 30, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and/or

c) a heavy chain that comprises the amino acid sequence of SEQ ID NO: 40, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

337. The kit of claim 327, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a) a first antigen-binding domain (D1) that binds a first epitope of human CD40; and

b) a second antigen-binding domain (D2) that binds a second epitope of human CD40.

338. The kit of claim 337, wherein the D1 domain and the D2 domain each comprise a heavy chain immunoglobulin variable region comprising a set of three heavy chain complementarity determining region sequences HCDR1, HCDR2, and HCDR3 independently selected from the group consisting of:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof;

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof; and

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof.

339. The kit of claim 337 or 338, wherein the D1 domain and the D2 domain each comprise a light chain immunoglobulin variable region comprising a set of three light chain complementarity determining region sequences LCDR1, LCDR2, and LCDR3, wherein the LCDR1 comprises the amino acid sequence of SEQ ID NO: 12, or a variant thereof, the LCDR2 comprises the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

340. The kit of any one of claims 337-339, wherein the D1 domain comprises:

a) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; or

b) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16 or a variant thereof; or

c) an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36 or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

341. The kit of claim 340, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

342. The kit of claim 341, wherein the D1 domain comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

343. The kit of claim 340, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

344. The kit of claim 343, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22, or a variant thereof.

345. The kit of claim 340, wherein the D1 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

346. The kit of claim 345, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

347. The kit of any one of claims 337-346, wherein the D1 domain comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

348. The kit of any one of claims 337-347, wherein the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12 or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

349. The kit of claim 348, wherein the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof.

350. The kit of any one of claims 337-347, wherein the D2 domain comprises an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

351. The kit of claim 350, wherein the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof.

352. The kit of any one of claims 348-351, wherein the D2 domain comprises an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

353. The kit of any one of claims 337-342, 347-349, and 352, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, or

a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

354. The kit of claim 353, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

355. The kit of any one of claims 337-340, 343-344, 347-349, and 352, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:

a D1 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 26, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 28, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof; and

a D2 domain comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, or a variant thereof, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, or a variant thereof, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16, or a variant thereof.

356. The kit of claim 355, wherein the D1 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 22 or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 domain comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

357. The kit of any one of claims 337-340, 345-347, and 350-352, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises:
a D1 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 34, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 38, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16; and
a D2 comprising an HCDR1 comprising the amino acid sequence of SEQ ID NO: 4, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 6, an HCDR3 comprising the amino acid sequence of SEQ ID NO: 8, an LCDR1 comprising the amino acid sequence of SEQ ID NO: 12, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 14, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

358. The kit of claim 357, wherein the D1 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 32, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof, and the D2 comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof, and an LCVR comprising the amino acid sequence of SEQ ID NO: 10, or a variant thereof.

359. The kit of any one of claims 322-358, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises a human IgG heavy chain constant region.

360. The kit of claim 359, wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

361. The kit of claim 360, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

362. The kit of claim 360, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

363. The kit of any one of claims 337-362, wherein the D1 domain comprises:
a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

364. The kit of any one of claims 337-363, wherein the D2 domain comprises:
a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; or
a heavy chain comprising the amino acid sequence of SEQ ID NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

365. The kit of any one of claims 337-364, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 42, or a variant thereof, and a light

chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

366. The kit of any one of claims 337-364, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 46, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 44, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

367. The kit of any one of claims 337-364, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 48, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

368. The kit of any one of claims 337-364, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 52, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

369. The kit of any one of claims 337-364, wherein the anti-CD40xCD40 bispecific antibody or the functional fragment thereof comprises (i) a D1 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 205, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof; and (ii) a D2 domain comprising a heavy chain comprising the amino acid sequence of SEQ ID

NO: 207, or a variant thereof, and a light chain comprising the amino acid sequence of SEQ ID NO: 20, or a variant thereof.

370. A method for inhibiting an immune response to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

371. A method for inhibiting generation of neutralizing antibodies to an immunogen in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

372. A method for preventing and/or suppressing an immunogen-specific T cell response in a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

373. The method of claim 372, wherein the prevention and/or suppression of the immunogen-specific T cell response comprises suppression of numbers and/or frequencies of the immunogen-specific T cells.

374. The method of claim 372 or 373, wherein the immunogen-specific T cells comprise follicular T helper cells (TFH) and/or CD4+ T cells.

375. The method of any one of claims 372-374, wherein the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or inflammation of an organ and/or a tissue in the subject in response to the immunogen.

376. The method of any one of claims 372-375, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle, and the prevention and/or suppression of the immunogen-specific T cell response comprises increasing or maintaining the level of transgene expression in the subject.

377. The method of claim 376, wherein the prevention and/or suppression of the immunogen-specific T cell response comprises prevention and/or suppression of injury and/or

inflammation of an organ and/or tissue in the subject in response to transgene expression in the organ and/or a tissue.

378. The method of any one of claims 375-377, wherein the tissue is muscle.

379. The method of any one of claims 375-377, wherein the organ is liver.

380. A method for increasing effectiveness of re-administration of an immunogen to a subject in need thereof, comprising administering to the subject an effective amount of a CD40L inhibitor.

381. The method of claim 380, wherein the immunogen re-administration occurs via the same administration route as its prior administration.

382. The method of claim 380, wherein the immunogen re-administration occurs via a different administration route than its prior administration.

383. The method of any one of claims 370-382, wherein the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

384. The method of any one of claims 370-382, wherein the method comprises determining the level of non-neutralizing antibodies in the subject.

385. The method of any one of claims 370-384, wherein the CD40L inhibitor is administered before the administration of the immunogen to the subject.

386. The method of any one of claims 370-384, wherein the CD40L inhibitor is administered simultaneously with the administration of the immunogen to the subject.

387. The method of any one of claims 370-384, wherein the CD40L inhibitor is administered after the administration of the immunogen to the subject.

388. The method of any one of claims 370-384, wherein the immunogen is administered to the subject two or more times and the CD40L inhibitor is administered before and/or between each of the administrations of the immunogen.

389. The method of any one of claims 370-388, wherein the subject has a preexisting immune response to the immunogen.

390. The method of any one of claims 370-388, further comprising administering to the subject an immunoglobulin depleting agent.

391. The method of claim 390, wherein the immunoglobulin depleting agent is administered before the administration of the CD40L inhibitor to the subject, and the CD40L inhibitor is administered before the administration of the immunogen to the subject.

392. The method of claim 390, wherein the CD40L inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, and the immunoglobulin depleting agent is administered before the administration of the immunogen to the subject.

393. The method of any one of claims 390-392, wherein the CD40L inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject has preexisting immunity against the immunogen.

394. The method of any one of claims 390-392, wherein the CD40L inhibitor and/or the immunoglobulin depleting agent is administered to the subject at a time when the subject does not have preexisting immunity against the immunogen.

395. The method of any one of claims 390-394, wherein the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40L inhibitor is resistant to said immunoglobulin degrading enzyme.

396. The method of claim 395, wherein the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, and HNSA-5487.

397. The method of claim 396, wherein the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

398. The method of any one of claims 370-397, further comprising administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogen.

399. The method of claim 398, wherein the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

400. The method of claim 398 or 399, wherein the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

401. The method of claim 400, wherein the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

402. The method of claim 401, wherein the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

403. The method of claim 402, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

404. The method of claim 403, wherein the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057,

a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

405. The method of claim 403 or 404, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

406. The method of claim 405, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

407. The method of any one of claims 403-406, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

408. The method of any one of claims 403-406, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

409. The method of any one of claims 402-408, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

410. The method of claim 409, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

411. The method of claim 409, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

412. The method of any one of claims 398-411, further comprising administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogen.

413. The method of claim 412, wherein the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

414. The method of claim 412 or 413, wherein the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

415. The method of any one of claims 412-414, wherein the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

416. The method of any one of claims 412-415, wherein the B cell depleting agent is an agent that binds to a B cell surface molecule.

417. The method of claim 416, wherein the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

418. The method of claim 417, wherein the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

419. The method of any one of claims 412-417, wherein the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

420. The method of claim 419, wherein the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

421. The method of claim 420, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

422. The method of claim 421, wherein the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid

sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

423. The method of claim 421 or 422, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

424. The method of claim 423, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

425. The method of any one of claims 421-424, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

426. The method of any one of claims 420-425, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

427. The method of claim 426, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

428. The method of claim 426, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

429. The method of any one of claims 412-415, wherein the B cell depleting agent is an agent targeting a B cell survival factor.

430. The method of any one of claims 412-415, wherein the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

431. The method of any one of claims 412-430, wherein the immunoglobulin depleting agent is capable of accelerating IgG clearance.

432. The method of any one of claims 412-431, wherein the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

433. The method of claim 432, wherein the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

434. The method of any one of claims 398-433, wherein the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

435. The method of any one of claims 398-434, wherein the plasma cell depleting agent is administered simultaneously with the immunogen, prior to the immunogen, or prior to and after the immunogen,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogen and the plasma cell depleting agent is administered if the immunogen is still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogen.

436. The method of any one of claims 398-435, wherein the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent is administered prior to the CD40L inhibitor.

437. The method of any one of claims 398-435, wherein the subject has preexisting immunity against the immunogen, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogen, wherein the plasma cell depleting agent and the CD40L inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogen when the plasma cell depleting agent and the CD40L inhibitor are administered.

438. The method of any one of claims 398-435, wherein:

(I) the subject does not have preexisting immunity against the immunogen before administration of a first dose of the immunogen, the CD40L inhibitor is administered prior to the first dose of the immunogen, the subject develops immunity against the immunogen from the first dose of the immunogen, and the plasma cell depleting agent is administered after the first dose of the immunogen but prior to a second dose of the immunogen; or

(II) the subject does not have preexisting immunity against the immunogen before administration of the immunogen, the CD40L inhibitor is administered prior to the immunogen, the subject develops immunity against the immunogen from the administration of the immunogen, and the plasma cell depleting agent is administered after the immunogen but prior to administration of a second immunogen.

439. The method of any one of claims 370-438, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

440. The method of claim 439, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

441. The method of claim 439, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

442. The method of any one of claims 370-438, wherein the immunogen is an immunoglobulin depleting agent.

443. The method of claim 442, wherein the immunoglobulin depleting agent is administered before the administration of the CD40L inhibitor to the subject at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

444. The method of claim 442, wherein the immunoglobulin depleting agent is administered before the administration of the CD40L inhibitor to the subject at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

445. The method of claim 442, wherein the CD40L inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject has preexisting immunity against the immunoglobulin depleting agent.

446. The method of claim 442, wherein the CD40L inhibitor is administered before the administration of the immunoglobulin depleting agent to the subject, at a time when the subject does not have preexisting immunity against the immunoglobulin depleting agent.

447. The method of any one of claims 442-446, wherein the immunoglobulin depleting agent is an immunoglobulin degrading enzyme, and the CD40L inhibitor is resistant to said immunoglobulin degrading enzyme.

448. The method of claim 447, wherein the immunoglobulin degrading enzyme is selected from Imlifidase/IdeS/Fabricator, IdeE, IdeZ, IdeXork, IceMG, CYR-212, CYR-241, S-1117, HNSA-5487 .

449. The method of claim 448, wherein the immunoglobulin degrading enzyme is Imlifidase/IdeS/Fabricator.

450. A method for increasing or maintaining the level of a transgene expression in a subject in need thereof, said method comprising administering to the subject an effective amount of a CD40L inhibitor.

451. The method of claim 450, wherein the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

452. The method of claim 450, wherein the method comprises determining the level of non-neutralizing antibodies in the subject.

453. The method of any one of claims 450-452, wherein the transgene is delivered to the subject via an immunogenic delivery vehicle.

454. The method of any one of claims 450-453, wherein the level of transgene expression is increased or maintained by inhibiting an immune response to the immunogenic delivery vehicle and/or by inhibiting an immune response to the transgene product(s).

455. The method of any one of claims 450-454, wherein the level of transgene expression is increased or maintained by inhibiting antibody responses to the transgene product(s).

456. The method of any one of claims 450-455, wherein the CD40L inhibitor is administered before the administration of the immunogenic delivery vehicle to the subject.

457. The method of any one of claims 450-455, wherein the CD40L inhibitor is administered simultaneously with the administration of the immunogenic delivery vehicle to the subject.

458. The method of any one of claims 450-455, wherein the CD40L inhibitor is administered after the administration of the immunogenic delivery vehicle to the subject.

459. The method of any one of claims 450-455, wherein the immunogenic delivery vehicle is administered to the subject two or more times and the CD40L inhibitor is administered before and/or between each of the administrations of the immunogenic delivery vehicle.

460. The method of any one of claims 450-459, wherein the subject has a preexisting immune response to the immunogenic delivery vehicle and/or to the transgene product(s).

461. The method of any one of claims 450-460, further comprising administering to the subject a plasma cell depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

462. The method of claim 461, wherein the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

463. The method of claim 461 or 462, wherein the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

464. The method of claim 463, wherein the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

465. The method of claim 464, wherein the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

466. The method of claim 465, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

467. The method of claim 466, wherein the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057,

a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

468. The method of claim 466 or 467, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

469. The method of claim 468, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

470. The method of any one of claims 466-469, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

471. The method of any one of claims 466-469, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

472. The method of any one of claims 465-471, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

473. The method of claim 472, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

474. The method of claim 472, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

475. The method of any one of claims 461-474, further comprising administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent at a time when the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s).

476. The method of claim 475, wherein the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

477. The method of claim 475 or 476, wherein the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

478. The method of any one of claims 475-477, wherein the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

479. The method of any one of claims 475-478, wherein the B cell depleting agent is an agent that binds to a B cell surface molecule.

480. The method of claim 479, wherein the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

481. The method of claim 480, wherein the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

482. The method of any one of claims 475-480, wherein the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

483. The method of claim 482, wherein the multispecific anti-CD20 antibody or functional fragment thereof is anti-CD20xCD3 bispecific antibody or functional fragment thereof.

484. The method of claim 483, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

485. The method of claim 484, wherein the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising

the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

486. The method of claim 484 or 485, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

487. The method of claim 486, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

488. The method of any one of claims 484-487, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

489. The method of any one of claims 483-488, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant

region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

490. The method of claim 489, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

491. The method of claim 489, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

492. The method of any one of claims 475-478, wherein the B cell depleting agent is an agent targeting a B cell survival factor.

493. The method of any one of claims 475-478, wherein the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

494. The method of any one of claims 475-493, wherein the immunoglobulin depleting agent is capable of accelerating IgG clearance.

495. The method of any one of claims 475-494, wherein the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

496. The method of claim 495, wherein the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

497. The method of any one of claims 461-496, wherein the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

498. The method of any one of claims 461-497, wherein the plasma cell depleting agent is administered simultaneously with the immunogenic delivery vehicle, prior to the immunogenic delivery vehicle, or prior to and after the immunogenic delivery vehicle,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the immunogenic delivery vehicle and the plasma cell depleting agent is administered if the immunogenic delivery vehicle and/or transgene product(s) are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior to the immunogenic delivery vehicle.

499. The method of any one of claims 461-498, wherein the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent is administered prior to the CD40L inhibitor.

500. The method of any one of claims 461-498, wherein the subject has preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s), and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the immunogenic delivery vehicle, wherein the plasma cell depleting agent and the CD40L inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the immunogenic delivery vehicle and/or to the transgene product(s) when the plasma cell depleting agent and the CD40L inhibitor are administered.

501. The method of any one of claims 461-498, wherein:

(I) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of a first dose of the immunogenic delivery vehicle, the CD40L inhibitor is administered prior to the first dose of the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene product(s) from the first dose of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the first dose of the immunogenic delivery vehicle but prior to administration of a second dose of the immunogenic delivery vehicle; or

(II) the subject does not have preexisting immunity against the immunogenic delivery vehicle and/or the transgene product(s) before administration of the immunogenic delivery vehicle, the CD40L inhibitor is administered prior to the immunogenic delivery vehicle, the subject develops immunity against the immunogenic delivery vehicle and/or the transgene

product(s) from the administration of the immunogenic delivery vehicle, and the plasma cell depleting agent is administered after the immunogenic delivery vehicle but prior to administration of a second immunogenic delivery vehicle.

502. The method of any one of claims 453-501, wherein the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

503. The method of claim 502, wherein the immunogenic delivery vehicle is a viral vector.

504. A method for increasing effectiveness of administration of a subsequently administered viral vector following administration of an originally administered viral vector in a subject in need thereof, said method comprising administering to the subject an effective amount of a CD40L inhibitor, wherein the subsequently administered viral vector is of the same or similar viral origin as the originally administered viral vector.

505. The method of claim 504, wherein the method comprises determining the presence of neutralizing antibodies to the immunogen in the subject.

506. The method of claim 504, wherein the method comprises determining the level of non-neutralizing antibodies in the subject.

507. The method of any one of claims 504-506, wherein the subsequently administered viral vector is administered via the same administration route as the originally administered viral vector.

508. The method of any one of claims 504-506, wherein the subsequently administered viral vector is administered via a different administration route from the originally administered viral vector.

509. The method of any one of claims 504-508, wherein the CD40L inhibitor is administered before the administration of the originally administered viral vector to the subject.

510. The method of any one of claims 504-508, wherein the CD40L inhibitor is administered simultaneously with the administration of the originally administered viral vector and/or subsequently administered viral vector to the subject.

511. The method of any one of claims 504-508, wherein the CD40L inhibitor is administered after the administration of the originally administered viral vector but before administering the subsequently administered viral vector to the subject.

512. The method of any one of claims 504-508, wherein the CD40L inhibitor is administered after the administration of the subsequently administered viral vector to the subject.

513. The method of any one of claims 504-508, wherein the CD40L inhibitor is administered before and/or between each of the subsequently administered administrations of the viral vectors to the subject.

514. The method of any one of claims 504-513, wherein the subject has a preexisting immune response to the viral vectors.

515. The method of any one of claims 504-514, further comprising administering to the subject a plasma cell depleting agent when the subject has preexisting immunity against the viral vectors.

516. The method of claim 515, wherein the plasma cell depleting agent is capable of depleting long-lived plasma cells (LLPC).

517. The method of claim 515 or 516, wherein the plasma cell depleting agent is a B cell maturation antigen (BCMA) targeting agent, optionally wherein the BCMA targeting agent is a chimeric antigen receptor (CAR) against BCMA or an anti-BCMA antibody or a functional fragment thereof, and optionally wherein the anti-BCMA antibody or functional fragment thereof is conjugated to a cytotoxic agent.

518. The method of claim 517, wherein the anti-BCMA antibody is a multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-BCMA antibody or functional fragment thereof targets BCMA and CD3.

519. The method of claim 518, wherein the multispecific anti-BCMA antibody or functional fragment thereof is anti-BCMAxCD3 bispecific antibody or functional fragment thereof, optionally wherein the anti-BCMAxCD3 bispecific antibody is selected from linvoseltamab (REGN5458), REGN5459, pacanalotamab (AMG420), teclistamab (JNJ-64007957), AMG701, alnuctamab (CC-93269), EM801, EM901, elranatamab (PF-06863135), TNB383B (ABBV-383), and TNB384B.

520. The method of claim 519, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to BCMA comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1055, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

521. The method of claim 520, wherein the first antigen-binding domain that specifically binds to BCMA comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1057, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1059, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1061, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

522. The method of claim 520 or 521, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence selected from the group consisting of SEQ ID NOs: 1079 and 1087, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1071.

523. The method of claim 522, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1081 or 1089, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1083 or 1091, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1085 or 1093, a

LCDR1 comprising the amino acid sequence of SEQ ID NO: 1073, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1075, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1077.

524. The method of any one of claims 520-523, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1081, 1083, and 1085, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

525. The method of any one of claims 520-523, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1057, 1059, and 1061, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1089, 1091, and 1093, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1073, 1075, and 1077, respectively.

526. The method of any one of claims 519-525, wherein the anti-BCMAxCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

527. The method of claim 526, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

528. The method of claim 526, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

529. The method of any one of claims 515-528, further comprising administering to the subject an effective amount of a B cell depleting agent and/or an immunoglobulin depleting agent when the subject has preexisting immunity against the viral vectors.

530. The method of claim 529, wherein the B cell depleting agent is administered before, at the same time as, or after the plasma cell depleting agent.

531. The method of claim 529 or 530, wherein the immunoglobulin depleting agent is administered after the plasma cell depleting agent.

532. The method of any one of claims 529-531, wherein the B cell depleting agent is capable of depleting B cells and plasma cells that express low levels of BCMA.

533. The method of any one of claims 529-532, wherein the B cell depleting agent is an agent that binds to a B cell surface molecule.

534. The method of claim 533, wherein the B cell depleting agent is selected from an anti-CD19 antibody, an anti-CD20 antibody, an anti-CD22 antibody, an anti-CD79 antibody, an anti-CD20xCD3 bispecific antibody, an anti-CD19xCD3 bispecific antibody, an anti-CD22xCD3 bispecific antibody, an anti-CD79xCD3 bispecific antibody, functional fragments of any of said antibodies, and any combinations thereof.

535. The method of claim 534, wherein the B cell depleting agent comprises an anti-CD20 antibody or a functional fragment thereof and an anti-CD19 antibody or a functional fragment thereof.

536. The method of any one of claims 529-534, wherein the B cell depleting agent is an anti-CD20 antibody or a functional fragment thereof, wherein the anti-CD20 antibody is a

multispecific antibody or a functional fragment thereof, optionally wherein the multispecific anti-CD20 antibody or functional fragment thereof targets CD20 and CD3.

537. The method of claim 536, wherein the multispecific anti-CD20 antibody or functional fragment thereof is an anti-CD20xCD3 bispecific antibody or functional fragment thereof.

538. The method of claim 537, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a first antigen-binding domain that specifically binds to CD20 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1097, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

539. The method of claim 538, wherein the first antigen-binding domain that specifically binds to CD20 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1100, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1101, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1102, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

540. The method of claim 538 or 539, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a second antigen-binding domain that specifically binds to CD3 comprising three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1099, and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1098.

541. The method of claim 540, wherein the second antigen-binding domain that specifically binds to CD3 comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 1106, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 1107, a HCDR3 comprising the amino acid sequence of SEQ ID NO: 1108, a LCDR1 comprising the amino acid sequence of SEQ ID NO: 1103, a LCDR2 comprising the amino acid sequence of

SEQ ID NO: 1104, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 1105.

542. The method of any one of claims 538-541, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises:

(a) a first antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1100, 1101, and 1102, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively; and

(b) a second antigen-binding domain that comprises HCDR1, HCDR2, and HCDR3 comprising the amino acid sequences of SEQ ID NOs: 1106, 1107, and 1108, respectively, and LCDR1, LCDR2, and LCDR3 comprising the amino acid sequences of SEQ ID NOs: 1103, 1104, and 1105, respectively.

543. The method of any one of claims 537-542, wherein the anti-CD20xCD3 bispecific antibody or functional fragment thereof comprises a human IgG heavy chain constant region, optionally wherein the human IgG heavy chain constant region is isotype IgG4 or IgG1.

544. The method of claim 543, wherein the human IgG heavy chain constant region comprises one or more modifications that increase binding to a neonatal Fc receptor (FcRn).

545. The method of claim 543, wherein the human IgG heavy chain constant region comprises one or more modifications that decrease binding to an Fc-gamma receptor (FcγR).

546. The method of any one of claims 529-532, wherein the B cell depleting agent is an agent targeting a B cell survival factor.

547. The method of any one of claims 529-532, wherein the B cell depleting agent is a BLyS/BAFF inhibitor, an APRIL inhibitor, a BLyS receptor 3/BAFF receptor inhibitor, or any combination thereof.

548. The method of any one of claims 529-547, wherein the immunoglobulin depleting agent is capable of accelerating IgG clearance.

549. The method of any one of claims 529-548, wherein the immunoglobulin depleting agent is a neonatal Fc receptor (FcRn) blocker.

550. The method of claim 549, wherein the FcRn blocker is selected from Efgartigimod (ARGX-113), Rozanolixizumab (UCB7665), Batoclimab (RVT-1401), IMVT-1402, Nipocalimab (M281), Orilanolimab (SYNT001), and any combinations thereof.

551. The method of any one of claims 515-550, wherein the method further comprises plasmapheresis, therapeutic plasma exchange, or immunoadsorption.

552. The method of any one of claims 515-551, wherein the plasma cell depleting agent is administered simultaneously with the viral vectors, prior to the viral vectors, or prior to and after the viral vectors,

optionally wherein the plasma cell depleting agent is administered within about 6 months after the viral vectors and the plasma cell depleting agent is administered if the viral vectors are still present in the subject, or

optionally wherein the plasma cell depleting agent is administered about 1 week prior to or within about 1 week prior the viral vectors.

553. The method of any one of claims 515-552, wherein the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent is administered prior to the CD40L inhibitor.

554. The method of any one of claims 515-552, wherein the subject has preexisting immunity against the viral vectors, and the plasma cell depleting agent and the CD40L inhibitor are both administered prior to the viral vectors, wherein the plasma cell depleting agent and the CD40L inhibitor are administered simultaneously, optionally wherein the subject has ongoing B cell responses to the viral vectors when the plasma cell depleting agent and the CD40L inhibitor are administered.

555. The method of any one of claims 515-552, wherein:

(I) the subject does not have preexisting immunity against the viral vectors before administration of a first dose of the viral vectors, the CD40L inhibitor is administered prior to the first dose of the viral vectors, the subject develops immunity against the viral vectors from the first dose of the viral vectors, and the plasma cell depleting agent is administered after the first dose of the viral vectors but prior to a second dose of the viral vectors; or

(II) the subject does not have preexisting immunity against the viral vectors before administration of the viral vectors, the CD40L inhibitor is administered prior to the viral vectors, the subject develops immunity against the viral vectors from the administration of the viral vectors, and the plasma cell depleting agent is administered after the viral vectors but prior to administration of second viral vectors.

556. The method of any one of claims 504-555, wherein the viral vectors are derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

557. The method of claim 556, wherein the viral vectors are derived from AAV.

558. The method of claim 557, wherein the subsequently administered AAV vector has a capsid derived from the same AAV serotype as the originally administered AAV vector.

559. The method of claim 556, wherein the retrovirus is a lentivirus.

560. The method of any one of claims 504-555, wherein the viral vectors are derived from an oncolytic virus.

561. The method of claim 560, wherein the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

562. The method of any one of claims 504-561, wherein the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof, a CD40L binding protein or a functional fragment thereof, or an oligonucleotide or a functional fragment thereof.

563. The method of claim 562, wherein the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof.

564. The method of claim 563, wherein the anti-CD40L antibody is an antagonistic anti-CD40L antibody or a functional fragment thereof.

565. The method of claim 563 or 564, wherein the anti-CD40L antibody is an anti-CD40L monospecific antibody or a functional fragment thereof.

566. The method of claim 563 or 564, wherein the anti-CD40L antibody is a multispecific antibody or a functional fragment thereof.

567. The method of any one of claims 563-566, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

568. The method of any one of claims 563-567, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 194, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof; and/or
an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof.

569. The method of any one of claims 563-568, wherein the anti-CD40L antibody or the functional fragment thereof comprises:

an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

570. The method of any one of claims 563-569, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
a heavy chain that comprises the amino acid sequence of SEQ ID NO: 201, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 202, or a variant thereof.

571. The method of claim 562, wherein the CD40L inhibitor is a CD40L-binding protein or a functional fragment thereof.

572. The method of claim 571, where in the CD40L-binding protein or the functional fragment thereof comprises the amino acid sequence of SEQ ID NO: 203, or a variant thereof.

573. The method of claim 572, wherein the CD40L-binding protein consists of the amino acid sequence of SEQ ID NO: 203.

574. A composition comprising an immunogen and a CD40L inhibitor and optionally further comprising a pharmaceutically acceptable carrier and/or excipient.

575. The composition of claim 574, wherein the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

576. The composition of claim 575, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

577. The composition of claim 575, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

578. The composition of claim 575, wherein the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

579. The composition of claim 578, wherein the immunogenic delivery vehicle is a viral vector.

580. The composition of claim 579, wherein the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, a retrovirus.

581. The composition of claim 580, wherein the viral vector is derived from AAV.

582. The composition of claim 580, wherein the retrovirus is a lentivirus.

583. The composition of claim 579, wherein the viral vector is derived from an oncolytic virus.

584. The composition of claim 583, wherein the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

585. The composition of any one of claims 574-584, wherein the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof, a CD40L binding protein or a functional fragment thereof, or an oligonucleotide or a functional fragment thereof.

586. The composition of claim 585, wherein the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof.

587. The composition of claim 586, wherein the anti-CD40L antibody is an antagonistic anti-CD40L antibody or a functional fragment thereof.

588. The composition of claim 586 or 587, wherein the anti-CD40L antibody is an anti-CD40L monospecific antibody or a functional fragment thereof.

589. The composition of claim 586 or 587, wherein the anti-CD40L antibody is a multispecific antibody or a functional fragment thereof.

590. The composition of any one of claims 586-589, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

591. The composition of any one of claims 586-590, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 194, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof; and/or
an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof.

592. The composition of any one of claims 586-591, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

593. The composition of any one of claims 586-592, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
a heavy chain that comprises the amino acid sequence of SEQ ID NO: 201, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 202, or a variant thereof.

594. The composition of claim 585, wherein the CD40L inhibitor is a CD40L-binding protein or a functional fragment thereof.

595. The composition of claim 594, where in the CD40L-binding protein or the functional fragment thereof comprises the amino acid sequence of SEQ ID NO: 203, or a variant thereof.

596. The composition of claim 595, wherein the CD40L-binding protein consists of the amino acid sequence of SEQ ID NO: 203.

597. A kit comprising (i) an immunogen, (ii) a CD40L inhibitor, and (iii) optionally, instructions for use.

598. The kit of claim 597, wherein the immunogen is an immunogenic delivery vehicle, and/or transgene product(s), a polypeptide, a polynucleotide, a glycan, or a lipid.

599. The kit of claim 598, wherein the immunogen is an immunogenic delivery vehicle and/or a polypeptide or polynucleotide encoded by a transgene contained within the immunogenic delivery vehicle.

600. The kit of claim 598, wherein the immunogen is an immunogenic delivery vehicle and/or transgene product(s).

601. The kit of claim 598, wherein the immunogenic delivery vehicle is a viral vector, a virus-like particle (VLP), a lipid nanoparticle (LNP), a non-lipid nanoparticle, a liposome, a bacterial vector, a fungal vector, or a protozoal vector.

602. The kit of claim 601, wherein the immunogenic delivery vehicle is a viral vector.

603. The kit of claim 602, wherein the viral vector is derived from an adeno-associated virus (AAV), an adenovirus, or a retrovirus.

604. The kit of claim 603, wherein the viral vector is derived from AAV.

605. The kit of claim 603, wherein the retrovirus is a lentivirus.

606. The kit of claim 602, wherein the viral vector is derived from an oncolytic virus.

607. The kit of claim 606, wherein the oncolytic virus is an adenovirus, a rhabdovirus, a herpes virus, a measles virus, a coxsackievirus, a poliovirus, a reovirus, a poxvirus, a parvovirus, Maraba virus, or Newcastle disease virus.

608. The kit of any one of claims 597-607, wherein the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof, a CD40L binding protein or a functional fragment thereof, or an oligonucleotide or a functional fragment thereof .

609. The kit of claim 608, wherein the CD40L inhibitor is an anti-CD40L antibody or a functional fragment thereof.

610. The kit of claim 609, wherein the anti-CD40L antibody is an antagonistic anti-CD40L antibody or a functional fragment thereof.

611. The kit of claim 609 or 610, wherein the anti-CD40L antibody is an anti-CD40L monospecific antibody or a functional fragment thereof.

612. The kit of claim 609 or 610, wherein the anti-CD40L antibody is a multispecific antibody or a functional fragment thereof.

613. The kit of any one of claims 609-612, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR comprising the HCDR1, HCDR2 and HCDR3 of an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR comprising the LCDR1, LCDR2 and LCDR3 of an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

614. The kit of any one of claims 609-613, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR that comprises: an HCDR1 comprising the amino acid of SEQ ID NO: 194, or a variant thereof, an HCDR2 comprising the amino acid sequence of SEQ ID NO: 195, or a variant thereof, and an HCDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof; and/or

an LCVR that comprises: an LCDR1 comprising the amino acid sequence of SEQ ID NO: 198, or a variant thereof, an LCDR2 comprising the amino acid sequence of SEQ ID NO: 199, or a variant thereof, and an LCDR3 comprising the amino acid sequence of SEQ ID NO: 200, or a variant thereof.

615. The kit of any one of claims 609-614, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
an HCVR that comprises the amino acid sequence of SEQ ID NO: 193, or a variant thereof; and an LCVR that comprises the amino acid sequence of SEQ ID NO: 197, or a variant thereof.

616. The kit of any one of claims 609-615, wherein the anti-CD40L antibody or the functional fragment thereof comprises:
a heavy chain that comprises the amino acid sequence of SEQ ID NO: 201, or a variant thereof, and a light chain that comprises the amino acid sequence of SEQ ID NO: 202, or a variant thereof.

617. The kit of claim 608, wherein the CD40L inhibitor is a CD40L-binding protein or a functional fragment thereof.

618. The kit of claim 617, where in the CD40L-binding protein or the functional fragment thereof comprises the amino acid sequence of SEQ ID NO: 203, or a variant thereof.

619. The kit of claim 618, wherein the CD40L-binding protein consists of the amino acid sequence of SEQ ID NO: 203.