

ENGINEERED IGA ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE

5 [0001] This application claims the benefit of U.S. Provisional Application No. 62/824,864, filed March 27, 2019; which is incorporated herein by reference in their entirety.

BACKGROUND OF THE DISCLOSURE

10 [0002] Monoclonal antibodies of IgG isotype targeting tumor antigens have proven to be an effective treatment of various cancers. Over the years an increasing number of monoclonal antibodies targeting different tumor antigens have been approved for use in cancer therapies. However, their clinical efficacy and side effects, especially as a monotherapy, are still insufficient. Therefore, it is of interest to develop new antibody therapies with increased clinical efficacy, novel targeting modalities or modes of action and/or decreased number and severity of side effects.

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SUMMARY OF THE DISCLOSURE

[0003] Provided herein is an antibody or a functional fragment thereof that comprises: an antigen binding domain; and a constant domain, wherein the constant domain comprises an immunoglobulin A (IgA) heavy chain constant region, wherein the IgA heavy chain constant region comprises an IgA CH2 region and an IgA CH3 region, wherein the IgA heavy chain constant region comprises a modification of at least two naturally occurring glycosylation sites, as compared to a corresponding wild type (WT) IgA heavy chain constant region, and wherein each of the at least two naturally occurring glycosylation sites is in the IgA CH2 region or in the IgA CH3 region.

20 [0003a] In one aspect, the present disclosure provides a pharmaceutical composition comprising an engineered immunoglobulin A subclass 2 (IgA2) antibody or a functional fragment thereof and a pharmaceutically acceptable carrier, diluent or excipient, wherein the engineered IgA2 antibody or functional fragment thereof comprises an antibody antigen binding domain; and an IgA2 heavy chain constant region, wherein the IgA2 heavy chain constant region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-21.

[0003b] In one aspect, the present disclosure provides a pharmaceutical composition comprising an engineered immunoglobulin A subclass 2 (IgA2) antibody or a functional fragment thereof and a pharmaceutically acceptable carrier, diluent or excipient, wherein the engineered IgA2 antibody or functional fragment thereof comprises an antibody antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region, wherein the IgA2 heavy chain constant region comprises an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, wherein a. the IgA2 CH1 region comprises an N45.2G amino acid substitution, and b. the IgA2 CH3 region comprises a deletion of residues P131 to Y148, each relative to a wildtype (WT) IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.

[0003c] In one aspect, the present disclosure provides the use of the composition as disclosed herein in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease in a subject.

[0003d] In one aspect, the present disclosure provides the use of the composition as disclosed herein in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease in a subject.

[0003e] In one aspect, the present disclosure provides the composition as disclosed herein for use as a medicament.

[0004] In some examples, the at least two naturally occurring glycosylation sites are two naturally occurring N-linked glycosylation sites. In some examples, one or more of the at least two naturally occurring glycosylation sites comprise a naturally occurring asparagine (N) amino acid residue which are modified in the engineered antibodies disclosed herein as compared to a corresponding wild type IgA. In some examples, the modification comprises an amino acid substitution, or an amino acid deletion of one, or both of the at least two naturally occurring glycosylation sites. In some examples, the amino acid substitution is a non-conservative amino acid substitution. In some examples, the IgA heavy chain constant region comprises an amino acid substitution at: i. N114 and N135, ii. N114 and N15.2, or iii. N135 and N15.2, relative to a corresponding WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises: i. a N114T amino acid substitution and a N135Q amino acid substitution, ii. a N114T amino acid substitution and an amino acid substitution selected from the group consisting of

N15.2G, N15.2Q, and N15.2T, or iii. a N135Q amino acid substitution and an amino acid substitution from the group consisting of N15.2G, N15.2Q, and N15.2T, relative to a corresponding WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0005] In some examples, the IgA heavy chain constant region comprises a modification of at least three naturally occurring glycosylation sites, as compared to a corresponding wild type IgA. In some examples, the at least three naturally occurring glycosylation sites are three N-linked glycosylation sites. In some examples, the three naturally occurring glycosylation sites each comprise an asparagine (N) amino acid residue which is modified in the antibodies described herein.

[0006] In some examples, the modification is an amino acid substitution or an amino acid deletion. In some examples, the amino acid substitution is a non-conservative substitution. In some examples, the IgA heavy chain constant region comprises an amino acid substitution at: N114, N135, and N15.2, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises: i. a N114T amino acid substitution, ii. a N135Q amino acid substitution, and iii. an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to the IMGT scheme.

[0007] In some examples, an IgA heavy chain constant region of an antibody described herein further comprises an IgA CH1 region. In some examples, the heavy chain constant region comprises a modification of at least one naturally occurring N-linked glycosylation site in the IgA CH2 region, at least one naturally occurring glycosylation site in the IgA CH3 regions, and at least one naturally occurring glycosylation site within the IgA CH1 region, as compared to a corresponding wild type IgA. In some examples, the IgA heavy chain constant region comprises an amino acid substitution at: i. N45.2, N114, and N135, or ii. N45.2, N15.2, and N135, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0008] In some examples, the IgA heavy chain constant region comprises: i. a N45.2G amino acid substitution, a N114T amino acid substitution, and a N135Q amino acid substitution; or ii. the N45.2G amino acid substitution, the N135Q amino acid substitution, and an amino acid substitution selected from a group consisting of N15.2G, N15.2Q, and N15.2T, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0009] In some examples, the heavy chain constant region of an antibody described herein comprises a modification of at least two naturally occurring N-linked glycosylation site in the IgA CH2 region, and at least one naturally occurring glycosylation site within the IgA CH1 region, as compared to a corresponding

wild type IgA. In some examples, the IgA heavy chain constant region comprises an amino acid substitution at: i. N45.2, N114, and N15.2G, numbering according to IMGT scheme. In some examples, described herein the IgA heavy chain constant region comprises: i. a N45.2G amino acid substitution, ii. a N114T amino acid substitution, and iii. an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme

[0010] In some examples, an antibody described herein or functional fragment thereof exhibits a greater circulating half-life compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation with serum proteins, compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof induces increased antibody dependent cell mediated cytotoxicity (ADCC), compared to a comparable antibody comprising an IgG heavy chain constant region. In some examples, the antibody or the functional fragment thereof exhibits increased thermostability, compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof exhibits decreased glycosylation, compared to a corresponding WT IgA antibody.

[0011] In some examples, the IgA heavy chain constant region exhibits binding to a Fc α R expressed on an immune effector cell with increased affinity, compared to a corresponding WT IgA antibody. In some examples, the IgA heavy chain constant region comprises a modification of at least four naturally occurring glycosylation sites, as compared to a corresponding wild type IgA. In some examples, the at least four naturally occurring glycosylation sites are four naturally occurring N-linked glycosylation sites. In some examples, the at least four naturally occurring glycosylation sites each comprise a naturally occurring asparagine (N) amino acid residue. In some examples, the heavy chain constant region comprises a modification of at least two naturally occurring N-linked glycosylation sites within the IgA CH2 region, at least one naturally occurring N-linked glycosylation sites within the IgA CH3 region, and at least one naturally occurring N-linked glycosylation site within the IgA CH1 region, as compared to a corresponding wild type IgA. In some examples, the IgA heavy chain constant region comprises an amino acid substitution at amino acid residues: N45.2, N114, N135, and N15.2, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0012] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a non-conservative amino acid substitution at amino acid residues: N45.2, N114, N135, and N15.2, numbering according to IMGT scheme.

[0013] In some examples, the IgA heavy chain constant region comprises: i. a N45.2G amino acid substitution, ii. a N114T amino acid substitution, iii. a N135Q amino acid substitution, and iv an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the antibody or the functional fragment thereof exhibits a greater circulating half-life compared to a corresponding IgA antibody comprising at least one naturally occurring N-linked glycosylation site. In some examples, the antibody or the functional fragment thereof induces increased antibody dependent cell mediated cytotoxicity (ADCC), compared to a corresponding comparable antibody comprising an IgG CH2 domain and an IgG CH3 domain. In some examples, the antibody or the functional fragment thereof exhibits increased thermostability, compared to a corresponding IgA antibody comprising at least one naturally occurring N-linked glycosylation site. In some examples, the antibody or the functional fragment thereof exhibits decreased glycosylation, compared to a corresponding IgA antibody comprising at least one naturally occurring N-linked glycosylation site. In some examples, the IgA heavy chain constant region exhibits binding to a FcαR expressed on an immune effector cell with increased affinity, compared to a corresponding IgA antibody comprising at least one naturally occurring N-linked glycosylation site.

[0014] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a modification of at least one naturally occurring cysteine (C) amino acid residue, as compared to a corresponding wild type IgA. In some examples, the modification is an amino acid substitution or an amino acid deletion of the at least one naturally occurring cysteine (C) amino acid residue. In some examples, the amino acid substitution is a non-conservative amino acid substitution of the at least one naturally occurring cysteine (C) amino acid residue. In some examples, the at least one naturally occurring cysteine amino acid residue is C147 or C86, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a C86S amino acid substitution, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a deletion of C147, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to the IMGT scheme. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation compared to a corresponding WT IgA antibody or the functional fragment thereof. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation with serum proteins compared to a corresponding WT IgA construct.

[0015] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a modification of at least two naturally occurring cysteine (C) amino acid residues, as compared to

a corresponding wild type IgA. In some examples, the modification comprises an amino acid substitution of one, or both of the at least two naturally occurring cysteine (C) amino acid residues. In some examples, the modification comprises a deletion of one, or both of the at least two naturally occurring cysteine (C) amino acid residues.

5 **[0016]** In some examples, the IgA heavy chain constant region comprises an amino acid substitution one of the at least two naturally occurring cysteine (C) amino acid residues, and a deletion of one of the at least two naturally occurring cysteine (C) amino acid residues. In some examples, the at least two naturally occurring cysteine amino acid residue are C147 and C86, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain
10 constant region comprises a deletion of C147, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises an amino acid substitution of C86, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NOs: 1, numbering according to IMGT scheme.

[0017] In some examples, the IgA heavy chain constant region of an antibody described herein comprises an
15 amino acid substitution of the naturally occurring C86 amino acid residue, and a deletion of the naturally occurring C147 amino acid residue, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises an C86S amino acid substitution, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the antibody or
20 the functional fragment thereof exhibits decreased aggregation compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation with serum proteins compared to a corresponding WT IgA antibody.

[0018] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a modification of at least one naturally occurring tyrosine (Y) amino acid residue, as compared to a corresponding
25 wild type IgA. In some examples, the modification is an amino acid substitution or a deletion of the at least one naturally occurring tyrosine (Y) amino acid residue. In some examples, the amino acid substitution is a non-conservative amino acid mutation of the at least one naturally occurring tyrosine (Y) amino acid residue, as compared to a WT IgA antibody. In some examples, the at least one tyrosine residue is Y148, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT
30 scheme. In some examples, the amino acid Y148 is deleted, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional

fragment thereof exhibits decreased aggregation with serum proteins compared to a corresponding WT IgA antibody.

[0019] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a modification of at least one naturally occurring threonine (T) amino acid residue, as compared to a corresponding wild type IgA antibody. In some examples, the modification comprises an amino acid substitution or deletion of the at least one naturally occurring threonine (T) amino acid residue, as compared to a corresponding wild type IgA antibody. In some examples, the amino acid substitution is a non-conservative amino acid substitution of the at least one naturally occurring threonine (T) amino acid residue. In some examples, the at least one naturally occurring threonine amino acid residue is T116 or T16, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof exhibits decreased aggregation with serum proteins compared to a corresponding WT IgA antibody. In some examples, the IgA heavy chain constant region comprises a modification of at least two naturally occurring threonine (T) amino acid residues, as compared to a corresponding wild type IgA. In some examples, the modification comprises an amino acid substitution or a deletion of one, or both the at least two naturally occurring threonine (T) amino acid residues. In some examples, the amino acid substitution is a non-conservative amino acid substitution of one, or both of the at least two naturally occurring threonine (T) amino acid residues. In some examples, the at least two naturally occurring threonine (T) amino acid residue are T116 or T16, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a T116S amino acid substitution, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a T16S amino acid substitution, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0020] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a modification of at least one naturally occurring isoleucine (I) amino acid residue, as compared to a corresponding wild type IgA. In some examples, the modification comprises an amino acid substitution or a deletion of the at least one naturally occurring isoleucine (I) amino acid residue. In some examples, the amino acid substitution comprises a non-conservative amino acid substitution of the at least one naturally occurring isoleucine (I) amino acid residue. In some examples, the at least one naturally occurring isoleucine (I) residue is I115, relative to the WT IgA heavy chain constant region comprising an amino acid

sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a H15L amino acid substitution, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a modification of at least one naturally occurring leucine (L) amino acid residue, as compared to a corresponding wild type IgA. In some examples, the modification comprises an amino acid substitution or a deletion of the at least one naturally occurring leucine (L) amino acid residue. In some examples, the amino acid substitution is a non-conservative amino acid substitution of the at least one naturally occurring leucine (L) amino acid residue. In some examples, the at least one naturally occurring leucine (L) residue is L15.3, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a L15.3I amino acid substitution, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0021] In some examples, the IgA heavy chain constant region of an antibody described herein comprises a modification of at least one naturally occurring proline (P) amino acid residue, as compared to a corresponding wild type IgA. In some examples, the IgA heavy chain constant region comprises an amino acid substitution or a deletion of the at least one naturally occurring proline (P) amino acid residue. In some examples, the amino acid substitution is a non-conservative amino acid substitution of the at least one naturally occurring proline (P) amino acid residue. In some examples, the at least one naturally occurring proline (P) residue is P124, relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a P124R amino acid substitution, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the antibody or functional fragment thereof exhibits greater stability, compared to a corresponding WT IgA antibody. In some examples, the antibody or the functional fragment thereof exhibits greater stability between a heavy chain and a light chain, compared to a corresponding WT IgA antibody. In some examples, the antibody or functional fragment thereof has a covalent linkage between the heavy chain and the light chain. In some examples, the antibody or the functional fragment thereof comprises a disulfide bond between a cysteine (C) amino acid residue of the heavy chain and a cysteine (C) amino acid residue of the light chain. In some examples, the IgA heavy chain constant region comprises an amino acid sequence selected from any one of SEQ ID NOs: 16-21.

[0022] In some examples, antibody described herein comprises a heavy chain region of a modified IgA of an allotype IgA2m(1) antibody or IgA2m(2). In some examples, the antibody is an allotype Caucasian IgA2m(1) antibody. In some examples, the IgA heavy chain constant region comprises a modification of a

C-terminal IgA tail piece, as compared to a corresponding wild type IgA. In some examples, the modification comprises a deletion of the C-terminal 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 12, 10, 8, 6, 4, or 2 amino acids. In some examples, the modification comprises a deletion of the C-terminal 18 amino acids. In some examples, the modification comprises a deletion of C-terminal amino acid residues 131-148, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA heavy chain constant region comprises a deletion of the C-terminal amino acid residues P131-Y148 relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0023] In some examples, the IgA heavy chain constant region of an antibody described herein comprises an IgA1 constant region comprising an IgA1 CH2 region and an IgA1 CH3 region. In some examples, the IgA1 constant region further comprises an IgA1 CH1 region. In some examples, the IgA heavy chain constant region comprises an IgA2 constant region comprising an IgA2 CH2 region and an IgA2 CH3 region. In some examples, the IgA2 constant region further comprises an IgA2 CH1 region. In some examples, the antibody or the functional fragment thereof exhibits a circulating half-life within 1%, 5%, 10%, 20%, or 30% of the circulating half-life of a corresponding antibody comprising the antigen binding domain and an IgA heavy chain constant region comprising an IgG CH2 region and an IgG CH3 region.

[0024] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region comprising an IgA2 CH1 region, IgA2 CH2 region and an IgA2 CH3 region; wherein the IgA2 heavy chain constant region comprises a N135Q amino acid substitution, numbering according to IMGT scheme, as compared to a corresponding relative to a WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1.

[0025] In some examples, the heavy chain constant region further comprises: a N45.2G amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, and an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T, relative to a WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the heavy chain constant region further comprises: a C86S amino acid substitution, a P124R amino acid substitution, a deletion of C147, a deletion of Y148, a L15.3I amino acid substitution, a T16S amino acid substitution, or a combination thereof, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0026] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region

comprising an IgA2 CH2 region and an IgA2 CH3 region, and wherein the IgA2 heavy chain constant region comprises: a C86S amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, and a N135Q amino acid substitution, relative to WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0027] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region comprising an IgA2 CH1 region, an IgA2 CH2 region, and an IgA CH3 region, and wherein the IgA2 heavy chain constant region comprises: a N45.2G amino acid substitution, a C86S amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, a N135Q amino acid substitution, a deletion of C147, and a deletion of Y148, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA2 heavy chain constant region comprises an amino acid sequence that is at least 95% identical to SEQ ID NO: 16.

[0028] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region comprising an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, and wherein the IgA2 heavy chain constant region comprises: a N45.2G amino acid substitution, a C86S amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, and a deletion of C-terminal tail piece, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

[0029] In some examples, the deletion of C-terminal tail piece comprises a deletion of C-terminal amino acid residues P131-Y148, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to the IMGT scheme.

[0030] In some examples, an IgA2 heavy chain constant region of an antibody described herein comprises an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6, 99.7%, 99.8%, 99.9% or 100% identical to SEQ ID NO: 17.

[0031] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region comprising an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region; wherein the IgA2 heavy chain constant region comprises: a N45.2G amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, a N135Q amino acid substitution, an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T, a L15.3I amino acid

substitution, and a T16S amino acid substitution, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to the IMGT scheme.

[0032] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region comprising an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, and wherein the IgA2 heavy chain constant region comprises: a N45.2G amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T, a L15.3I amino acid substitution, a T16S amino acid substitution, and a deletion of C-terminal amino acids P131-Y148, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to the IMGT scheme.

[0033] In some examples, an antibody or the functional fragment thereof disclosed herein comprising: a C86S amino acid substitution, a P124R amino acid substitution, a deletion of C147, a deletion of Y148, or a combination thereof, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA2 heavy chain constant region comprises an amino acid sequence that is at least 95% identical to a sequence selected from any one of SEQ ID NOs: 18-21. In some examples, the antibody or the functional fragment thereof is aglycosylated. In some examples, the antibody or the functional fragment thereof has increased circulatory half life than a corresponding IgA comprising one or more of wild type amino acid residues N45.2, N114, I115, T116, N15.2, L15.3, T16, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme.

[0034] In some examples, an antibody or functional fragment thereof described herein induces increased antibody dependent cell mediated cytotoxicity (ADCC), compared to a corresponding antibody comprising an IgG heavy chain constant domain. In some examples, the antibody or the functional fragment thereof exhibits increased thermostability, compared to a corresponding IgA comprising one or more of wild type amino acid residues N45.2, N114, I115, T116, N15.2, L15.3, T16, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme, numbering according to the IMGT scheme. In some examples, the antibody or the functional fragment thereof exhibits decreased glycosylation, compared to a corresponding IgA comprising one or more of wild type amino acid residues N45.2, N114, I115, T116, N15.2, L15.3, T16, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme. In some examples, the IgA heavy chain constant region exhibits binding to Fc α R expressed on an immune effector cell with increased affinity, compared to a comprising one or more of wild type amino acid residues N45.2, N114, I115, T116, N15.2, L15.3, T16, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme. In some examples, the IgA heavy chain constant region

further comprises a hinge region. In some examples, the hinge region comprises an IgA hinge amino acid sequence or a variant or a fragment thereof. In some examples, the hinge region comprises a human IgA hinge amino acid sequence or a variant or a fragment thereof. In some examples, the hinge is an IgA1 hinge or an IgA2 hinge, or a variant or a fragment thereof. In some examples, the constant domain further comprises a light chain constant region. In some examples, the light chain constant region is a kappa light chain constant region, wherein the kappa light chain constant region comprises a sequence of SEQ ID NO: 31. In some examples, the IgA heavy chain constant region further comprises one or more albumin binding regions. In some examples, the one or more albumin binding domains are fused to the C-terminus of the CH3 region. In some examples, the constant region comprises the light chain constant region and the one or more albumin binding domain is fused to the light chain constant region. In some examples, the antibody or the functional fragment thereof has a greater circulating half-life compared to a corresponding IgA antibody that does not comprise the one or more albumin binding domains. In some examples, the antibody or the functional fragment thereof exhibits decreased complement-dependent cytotoxicity (CDC) compared to a corresponding antibody comprising an IgG heavy chain constant domain when measured in a suitable in vitro CDC assay.

[0035] In some examples, an antibody or functional fragment thereof described herein exhibits increased antibody-dependent cell-mediated cytotoxicity (ADCC) compared to a corresponding WT IgA antibody when measured in a suitable in vitro ADCC assay. In some examples, the antigen binding domain comprises a heavy chain variable region and a light chain variable region. In some examples, the heavy chain variable region of an antibody described herein comprises at least one of complementarity determining regions (CDRs): HC-CDR1 comprising an amino acid sequence selected from any one of SEQ ID NOs: 33-40, HC-CDR2 comprising an amino acid sequence selected from any one of SEQ ID NOs: 41-48; and HC-CDR3 comprising an amino acid sequence selected from any one of SEQ ID NOs: 49-56.

[0036] In some examples, the light chain variable region of an antibody described herein comprises at least one of complementarity determining regions (CDRs): LC-CDR1 comprising an amino acid sequence selected from any one of SEQ ID NOs: 57-64; LC-CDR2 comprising an amino acid sequence selected from any one of SEQ ID NOs: 65-72; and LC-CDR3 comprising an amino acid sequence selected from any one of SEQ ID NOs: 73-80.

[0037] In some examples, the heavy chain variable region of an antibody described herein comprises a sequence having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or 100% identity to an amino acid sequence selected from any one of SEQ ID NOs: 4, 7, 81-86. In some examples, the light chain variable region comprises a sequence having at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9% or 100% identity to an amino acid sequence selected from any one of SEQ ID NOs: 5, 8, 95-

100. In some examples, each of the heavy chain and light chain CDRs are derived from an IgG antibody. In some examples, the heavy chain variable region further comprises four framework regions (FWs): HC-FW1, HC-FW2, HC-FW3, and HC-FW4. In some examples, the light chain variable region further comprises four framework regions (FWs): LC-FW1, LC-FW2, LC-FW3, and LC-FW4.

5 **[0038]** In some examples, each the heavy chain and light chain FW regions are derived from an IgG antibody. In some examples, each the heavy chain and light chain FW regions are derived from an IgA antibody.

[0039] In some examples, an antibody described herein or the functional fragment thereof is a chimeric antibody, a heavy chain antibody, a single chain antibody, a humanized antibody, a human antibody, a monoclonal antibody, a deimmunized antibody, a bispecific antibody, a multispecific antibody, a multivalent antibody, or a combination thereof.

10 **[0040]** In some examples, the antigen-binding fragment of an antibody described herein comprises a Fab, Fab', Fab'-SH, Fv, scFv, F(ab')₂, a diabody, a linear antibody, a single domain antibodies (sdAb), a VHH domain, or a multi-specific antibody formed from antibody fragments. In some examples, the variable domain specifically binds to GD2, CD20, CD47, CD38, CD19, EGFR, HER2, PD-L1, or CD25. In some examples, the antibody or the functional fragment thereof further comprises an enzyme, a substrate, cofactor, a fluorescent marker, a chemiluminescent marker, a peptide tag, a magnetic particle, a drug, a toxin, a radionuclide, a binding site for secondary antibodies, a metal binding domain, or a combination thereof.

15 **[0041]** Provided herein is a pharmaceutical composition of comprising the antibody or the functional fragment thereof of any one of aspects above and a pharmaceutically acceptable carrier.

20 **[0042]** Provided herein is a method of treating or a composition for use in treating a subject in need thereof, comprising administering to the subject a therapeutic dose of the antibody or the functional fragment thereof of any one of aspects above or the pharmaceutical composition disclosed above.

[0043] In some examples, the antibody or the functional fragment thereof or the pharmaceutical composition is cytolytic to a target cell. In some examples, the target cell is a cancer cell. In some examples, the antibody or the functional fragment thereof or the pharmaceutical composition inhibits tumor growth. In some examples, the antibody or the functional fragment thereof or the pharmaceutical composition is administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially. In some examples, the antibody or the functional fragment thereof or the pharmaceutical composition is administered to the subject in combination with a second therapeutic agent. In some examples, the second therapeutic agent comprises an anti-cancer agent, a chemotherapeutic agent, radiation therapy, a cytotoxic agent, a NSAID, a corticosteroid, a dietary supplement such as an antioxidant, or a combination thereof. In some examples, the second therapeutic agent is administered

prior to, concurrently, or after administering the antibody or the functional fragment thereof or the pharmaceutical composition.

[0044] Provided herein is an isolated nucleic acid encoding the antibody or the functional fragment thereof of any one of aspects above.

5 **[0045]** Provided herein is an isolated nucleic acid molecule encoding a heavy chain polypeptide, the isolated nucleic acid molecule comprising a first nucleic acid sequence encoding a IgA heavy chain constant region, wherein the first nucleic acid sequence is selected from any one of SEQ ID NOs: 25-32. In some examples, the isolated nucleic acid molecule aspect above, further comprises a second nucleic acid sequence encoding a variable heavy chain region, wherein the second nucleic acid sequence is selected from any one of SEQ ID
10 NOs:87-84.

[0046] Provided herein is a vector comprising the isolated nucleic acid molecule of any one of aspects above.

[0047] Provided herein is a host cell comprising the isolated nucleic acid molecule of any one of aspects above. In some examples, the host cell of any one of aspects above, further comprises an isolated nucleic acid molecule encoding a light chain polypeptide, wherein the isolated nucleic acid molecule encoding the light
15 chain polypeptide comprises a nucleic acid sequence encoding a variable light chain region, wherein the nucleic acid sequence is selected from any one of SEQ ID NOs:101-108. In some examples, the isolated nucleic acid molecule encoding the light chain polypeptide further comprises a nucleic acid sequence encoding a kappa light chain constant region, wherein the nucleic acid sequence comprises a sequence of SEQ ID NO:32.

20 **[0048]** Provided herein is a host cell expressing the antibody or the functional fragment thereof of any one of aspects above. In some examples, the host cell is a bacterial cell or a mammalian cell. In some examples, the host cell is a CHO cell, or a HEK293 cell.

[0049] Provided herein is a method of producing an antibody or the functional fragment thereof, the method comprising: (a) culturing the host cell of any one of aspects above in a medium under conditions permitting
25 expression of a polypeptide encoded by the isolated nucleic acid molecule and assembling of the antibody or the functional fragment thereof; and (b) purifying the antibody or the functional fragment thereof from the cultured host cell or the medium of the host cell. In some examples, the purifying is by size exclusion chromatography.

[0050] Provided herein is an antibody or a functional fragment thereof that selectively binds to a CD20
30 polypeptide or a variant thereof, comprising: (a) an IgA heavy chain constant region, wherein the IgA heavy chain constant region comprises an amino acid sequence selected from any one of SEQ ID NOs:16-21; and (b) a variable heavy chain region, wherein the variable heavy chain region comprises at least one of a complementarity-determining region heavy chain 1 (HC-CDR1) of SEQ ID NO: 33, HC-CDR2 of SEQ ID NO: 41, and HC-CDR3 of SEQ ID NO: 49; (c) a variable light chain region, wherein the variable light chain

region comprises at least one of a complementarity-determining region light chain 1 (LC-CDR1) of SEQ ID NO:57, LC-CDR2 of SEQ ID NO:65, and LC-CDR3 of SEQ ID NO:73; or (d) the variable heavy chain of (b) and the variable light chain of (c). In some examples, the variable heavy chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 81, and the variable light chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 95.

[0051] Provided herein is an antibody or a functional fragment thereof that selectively binds to a GD2 protein or a variant thereof, comprising: (a) an IgA heavy chain constant region, wherein the IgA heavy chain constant region comprises an amino acid sequence selected from any one of SEQ ID NOs: 16-21; and (b) a variable heavy chain region, wherein the variable heavy chain region comprises at least one of a complementarity-determining region heavy chain 1 (HC-CDR1) of SEQ ID NO: 34, HC-CDR2 of SEQ ID NO: 42, and HC-CDR3 of SEQ ID NO: 50; (c) a variable light chain region, wherein the variable light chain region comprises at least one of a complementarity-determining region light chain 1 (LC-CDR1) of SEQ ID NO: 58, LC-CDR2 of SEQ ID NO: 66, and LC-CDR3 of SEQ ID NO: 74; or (d) the variable heavy chain of (b) and the variable light chain of (c). In some examples, the variable heavy chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 4, and the variable light chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 5.

[0052] Provided herein is an antibody or a functional fragment thereof that selectively binds to a Her2 protein or a variant thereof, comprising: (a) an IgA heavy chain constant region, wherein the IgA heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 16-21; and (b) a variable heavy chain region, wherein the variable heavy chain region comprises at least one of a complementarity-determining region heavy chain 1 (HC-CDR1) of SEQ ID NO: 35, HC-CDR2 of SEQ ID NO: 43, and HC-CDR3 of SEQ ID NO: 51; (c) a variable light chain region, wherein the variable light chain region comprises at least one of a complementarity-determining region light chain 1 (LC-CDR1) of SEQ ID NO: 59, LC-CDR2 of SEQ ID NO: 67, and LC-CDR3 of SEQ ID NO: 75; or (d) the variable heavy chain of (b) and the variable light chain of (c). In some examples, the variable heavy chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 82, and the variable light chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 96.

[0053] Provided herein is an antibody or a functional fragment thereof that selectively binds to a gp75 protein or a variant thereof, comprising: (a) an IgA heavy chain constant region, wherein the IgA heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 16-21; and (b) a variable heavy chain region, wherein the variable heavy chain region comprises at least one of a complementarity-

determining region heavy chain 1 (HC-CDR1) of SEQ ID NO: 36, HC-CDR2 of SEQ ID NO: 44, and HC-CDR3 of SEQ ID NO: 52; (c) a variable light chain region, wherein the variable light chain region comprises at least one of a complementarity-determining region light chain 1 (LC-CDR1) of SEQ ID NO: 60, LC-CDR2 of SEQ ID NO: 68, and LC-CDR3 of SEQ ID NO: 76; or (d) the variable heavy chain of (b) and the variable light chain of (c). In some examples, the variable heavy chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 83, and the variable light chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 97.

[0054] Provided herein is an antibody or a functional fragment thereof that selectively binds to a CTLA4 protein or a variant thereof, comprising: (a) an IgA heavy chain constant region, wherein the IgA heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 16-21; and (b) a variable heavy chain region, wherein the variable heavy chain region comprises at least one of a complementarity-determining region heavy chain 1 (HC-CDR1) of SEQ ID NO: 37, HC-CDR2 of SEQ ID NO: 45, and HC-CDR3 of SEQ ID NO: 53; (c) a variable light chain region, wherein the variable light chain region comprises at least one of a complementarity-determining region light chain 1 (LC-CDR1) of SEQ ID NO: 61, LC-CDR2 of SEQ ID NO: 69, and LC-CDR3 of SEQ ID NO: 77; or (d) the variable heavy chain of (b) and the variable light chain of (c). In some examples, the variable heavy chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 84, and the variable light chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 98.

[0055] Provided herein is an antibody or a functional fragment thereof that selectively binds to a CD47 protein or a variant thereof, comprising: (a) an IgA heavy chain constant region, wherein the IgA heavy chain constant region comprises an amino acid sequence selected from SEQ ID NOs: 16-21; and (b) a variable heavy chain region, wherein the variable heavy chain region comprises at least one of a complementarity-determining region heavy chain 1 (HC-CDR1) of SEQ ID NO: 38, HC-CDR2 of SEQ ID NO: 46, and HC-CDR3 of SEQ ID NO: 54; (c) a variable light chain region, wherein the variable light chain region comprises at least one of a complementarity-determining region light chain 1 (LC-CDR1) of SEQ ID NO: 62, LC-CDR2 of SEQ ID NO: 70, and LC-CDR3 of SEQ ID NO: 78; or (d) the variable heavy chain of (b) and the variable light chain of (c). In some examples, the variable heavy chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 85, and the variable light chain comprises a polypeptide sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 99.

[0056] Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region

comprising an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, and wherein the IgA2 heavy chain constant region comprises: a N45.2G amino acid substitution, a N135Q amino acid substitution, a deletion of C147, and a deletion of Y148, relative to the WT IgA2 heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme.

5 **[0057]** Provided herein is an antibody or a functional fragment thereof comprising: an antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region comprising an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, and wherein the IgA2 heavy chain constant region comprises: a N45.2G amino acid substitution, a N114T amino acid substitution, a I115L amino acid substitution, a T116S amino acid substitution, an amino acid substitution selected from the group consisting of
10 N15.2G, N15.2Q, and N15.2T, and a deletion of C-terminal amino acids P131-Y148, relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to the IMGT scheme.

[0058] In some examples, the antibody or the functional fragment thereof of aspect above, further comprises: a C86S amino acid substitution, a P124R amino acid substitution, a deletion of C147, a deletion of Y148, a L15.3I
15 amino acid substitution, a T16S amino acid substitution or a combination thereof,

[0059] relative to the WT IgA heavy chain constant region comprising an amino acid sequence of SEQ ID NO: 1, numbering according to IMGT scheme. In some examples, the IgA2 heavy chain constant region comprises an amino acid sequence that is at least 95% identical to a sequence selected from any one of SEQ ID NOs: 18-21. In some examples the antibody or the functional fragment thereof is aglycosylated.

20 **[0060]** In some examples the antibody or the functional fragment thereof has increased circulatory half-life than a corresponding IgA comprising one or more of wild type amino acid residues N45.2, N114, I115, T116, N15.2, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme.

[0061] In some examples the antibody or the functional fragment thereof induces increased antibody dependent cell mediated cytotoxicity (ADCC), compared to a corresponding antibody comprising an IgG heavy chain
25 constant domain. In some examples the antibody or the functional fragment thereof exhibits increased thermostability, compared to a corresponding IgA comprising one or more of wild type amino acid residues N45.2, N114, I115, T116, N15.2, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme, numbering according to the IMGT scheme. In some examples the antibody or the functional fragment thereof exhibits decreased glycosylation, compared to a corresponding IgA comprising one or more of wild type
30 amino acid residues N45.2, N114, I115, T116, N15.2, or a C-terminal amino acid residues P131-Y148, numbering according to the IMGT scheme.

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising an engineered immunoglobulin A subclass 2 (IgA2) antibody or a functional fragment thereof and a pharmaceutically acceptable carrier, diluent or excipient, wherein the engineered IgA2 antibody or a functional fragment thereof comprises an antibody antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region, wherein the IgA2 heavy chain constant region comprises an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, wherein the IgA2 CH3 region comprises:
 - a. an N135Q amino acid substitution, and
 - b. a deletion of C147 and Y148,
 each relative to a wildtype (WT) IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11 .
2. The pharmaceutical composition of claim 1, wherein the IgA2 CH1 region comprises an amino acid substitution at P124, relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11 .
3. The pharmaceutical composition of claim 2, wherein the amino acid substitution at P124 is P124R, relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.
4. The pharmaceutical composition of claim 1, wherein the IgA2 CH1 region comprises an amino acid substitution at N45.2, relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.
5. The pharmaceutical composition of claim 4, wherein the amino acid substitution at N45.2 is N45.2G or N45.2A, relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.
6. A pharmaceutical composition comprising an engineered immunoglobulin A subclass 2 (IgA2) antibody or a functional fragment thereof and a pharmaceutically acceptable carrier, diluent or excipient, wherein the engineered IgA2 antibody or functional fragment thereof comprises an antibody

antigen binding domain; and an IgA2 heavy chain constant region, wherein the IgA2 heavy chain constant region comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 16-21.

- 5 7. The pharmaceutical composition of claim 1, wherein the IgA2 CH2 region comprises an Asn to Gly, an Asn to Gln, or an Asn to Thr amino acid substitution corresponding to amino acid residue 23 of SEQ ID NO: 110.
- 10 8. The pharmaceutical composition of claim 1, wherein the IgA2 CH2 region comprises at least one amino acid substitution of a residue corresponding to any one of amino acid residues 97, 98, and 99 of SEQ ID NO: 110.
- 15 9. The pharmaceutical composition of claim 1, wherein the IgA2 CH2 region comprises at least one amino acid substitution of a residue corresponding to amino acid residue 24 or 25 of SEQ ID NO: 110.
- 20 10. A pharmaceutical composition comprising an engineered immunoglobulin A subclass 2 (IgA2) antibody or a functional fragment thereof and a pharmaceutically acceptable carrier, diluent or excipient, wherein the engineered IgA2 antibody or functional fragment thereof comprises an antibody antigen binding domain; and a constant domain, wherein the constant domain comprises an IgA2 heavy chain constant region, wherein the IgA2 heavy chain constant region comprises an IgA2 CH1 region, an IgA2 CH2 region, and an IgA2 CH3 region, wherein
- 25 a. the IgA2 CH1 region comprises an N45.2G amino acid substitution, and
- b. the IgA2 CH3 region comprises a deletion of residues P131 to Y148,
- each relative to a wildtype (WT) IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.
- 30 11. The pharmaceutical composition of claim 10, wherein the IgA2 CH1 region comprises an amino acid substitution at P124, relative to a wildtype (WT) IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.
12. The pharmaceutical composition of claim 11, wherein the amino acid substitution at P124 is P124R, relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.

13. The pharmaceutical composition of claim 10, wherein the IgA2 CH2 region comprises an Asn to Gly, an Asn to Gln, or an Asn to Thr amino acid substitution corresponding to amino acid residue 23 of SEQ ID NO: 110.

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14. The pharmaceutical composition of claim 10, wherein the IgA2 CH2 region comprises at least one amino acid substitution of a residue corresponding to any one of amino acid residues 97, 98, and 99 of SEQ ID NO: 110.

10 15. The pharmaceutical composition of claim 10, wherein the IgA2 CH2 region comprises at least one amino acid substitution of a residue corresponding to amino acid residue 24 or 25 of SEQ ID NO: 110.

15 16. Use of the composition of claim 1 in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease in a subject.

17. Use of the composition of claim 10 in the manufacture of a medicament for treating a cancer, an infectious disease, or an autoimmune disease in a subject.

20 18. The composition of claim 1 or 10 for use as a medicament.

19. The pharmaceutical composition of claim 10, wherein the IgA2 heavy chain constant region further comprises

- 25
- a. a C86S amino acid substitution,
 - b. a N114T amino acid substitution,
 - c. a I115L amino acid substitution, and
 - d. a T116S amino acid substitution;

relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.

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20. The pharmaceutical composition of claim 10, wherein the IgA2 heavy chain constant region further comprises

- a. a N114T amino acid substitution,
- b. a I115L amino acid substitution,

c. a T116S amino acid substitution,
d. an amino acid substitution selected from the group consisting of N15.2G, N15.2Q, and N15.2T,

e. a L15.3I amino acid substitution, and

5 f. a T16S amino acid substitution;

relative to the WT IgA heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 1, numbering according to Table 11.