METHODS AND COMPOSITIONS FOR PREVENTION OF TRANSPLANT REJECTION

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Patent Application No. 63/603,591, filed November 28, 2023; and to U.S. Provisional Patent Application No. 63/643,866, filed May 7, 2024; which applications are incorporated by reference herein in their entirety.

REFERENCE TO THE SEQUENCE LISTING

[0002] This application contains a Sequence Listing in computer readable format. The Sequence Listing is provided as a file entitled 5577_008PC03_SequenceListing_ST26.xml created November 27, 2024, which is 119,067 bytes in size. The information in the computer readable form of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Field

[0003] The present disclosure relates to methods and compositions for treating an autoimmune disorder in a subject, including, for example, a kidney-related autoimmune disorder, such as kidney-related diseases, disorders, or complications, such as Berger's Disease or renal transplantation, and for preventing transplant rejections. Also provided are methods of increasing or improving kidney transplant function.

Background

[0004] The kidneys are essential organs for filtering blood and regulating the mineral content in a subject. Many diseases and disorders are associated with the kidney, including chronic kidney disease (CKD), diabetic kidney disease, acute kidney injury, kidney failure, polycystic kidney disease (PCKD), hematuria, Fabry disease, lupus

kidney disease, Alport's syndrome, IgM nephropathy, interstitial nephritis, Membranoproliferative Glomerulonephritis, simple kidney cysts, kidney infections, kidney stones, and IgA nephropathy.

[0005] Severe kidney disease in an individual can result in the need for a kidney organ transplant. However, the individual typically must receive the donated kidney from a donor that is ABO blood group and crossmatch (human leukocyte antigen – HLA) compatible. Even with a successful transplant of a suitable kidney, the individual must remain on immunosuppressants for the remainder of their lives. Otherwise, their immune system runs a high risk of rejecting the new organ. Further still, the use of immunosuppressants is not without risk. An immunosuppressive regimen typically contains calcineurin inhibitors, and long-term use of calcineurin inhibitors is associated with nephrotoxicity and subsequent graft failure, as well as other adverse events, including hypertension, hyperlipidemia, and diabetes mellitus.

[0006] Even with an immunosuppressive regimen, some kidney transplants will nevertheless fail, with graft survival rates declining over a period of 1 year, 5 years, or 10 years post-transplant. Estimated glomerular filtration rate (eGFR) at 12 months post-transplant is strongly associated with subsequent graft failure. For example, an eGFR < 50 mL/min/1.73 m^2 is associated with lower graft survival. Thus, there is a need for increasing kidney graft survival by ensuring that the recipients's eGFR remains above 50 mL/min/1.73 m^2 following transplant.

BRIEF SUMMARY

[0007] The present disclosure provides methods of improving transplanted kidney function in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the transplanted kidney function is measured by an aggregate mean estimated glomerular filtration rate (eGFR) and is improved relative to a control.

[0008] In some embodiments, the control is a kidney transplant under the standard of care of tacrolimus. In some embodiments, the improvement of eGFR is by at least or about 10% relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the improvement of eGFR is by at least or about 20% relative to a

kidney transplant under the standard of care of tacrolimus. In some embodiments, the improvement of eGFR is an increase by at least 5 mL/min/1.73 m^2 relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the improvement of eGFR is an increase by at least 10 mL/min/1.73 m^2 relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the improvement of eGFR is an increase by at least 15 mL/min/1.73 m^2 relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the improvement of eGFR is to at least 50 mL/min/1.73 m^2 after 90 days following the administering. In some embodiments, the improvement of eGFR is to at least 60 mL/min/1.73 m^2 after 90 days following the administering. In some embodiments, the improvement of eGFR is to at least 70 mL/min/1.73 m^2 after 90 days following the administering. In some embodiments, the improvement of eGFR is to at least 80 mL/min/1.73 m^2 after 90 days following the administering. In some embodiments, the improvement of eGFR is to at least 50 mL/min/1.73 m^2 after 1 year following the administering. In some embodiments, the improvement of eGFR is to at least 60 mL/min/1.73 m^2 after 1 year following the administering. In some embodiments, the improvement of eGFR is to at least 70 mL/min/1.73 m^2 after 1 year following the administering. In some embodiments, the improvement of eGFR is to at least 80 mL/min/1.73 m^2 after 1 year following the administering. In some embodiments, the improvement of eGFR is to at least 90 mL/min/1.73 m^2 after 1 year following the administering. In some embodiments, the methods further comprise restoring kidney function to a normal level following kidney transplant as measured by eGFR.

[0009] The present disclosure also provides methods of preventing or reducing kidney transplant rejection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the method prevents or reduces kidney transplant rejection in the subject for greater than a year after transplant as measured by an aggregate mean estimated glomerular filtration rate (eGFR). In some embodiments, the eGFR greater than a year after transplant is at least 50 mL/min/1.73 m^2. In some embodiments, the eGFR greater than a year after transplant is at least 60 mL/min/1.73 m^2. In some embodiments, the eGFR greater than a year after transplant is at least 70 mL/min/1.73 m^2. In some embodiments, the eGFR greater

than a year after transplant is at least 80 mL/min/1.73 m^2. In some embodiments, the eGFR greater than a year after transplant is at least 90 mL/min/1.73 m^2.

[0010] The present disclosure also provides methods of delaying kidney transplant rejection in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the delaying kidney transplant rejection is relative to a control. In some embodiments, the control is a kidney transplant under the standard of care of tacrolimus. In some embodiments, the delaying of kidney transplant rejection is 10% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the delaying of kidney transplant rejection is 20% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the delaying of kidney transplant rejection is 30% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the delaying of kidney transplant rejection is 40% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the delaying of kidney transplant rejection is 50% or more relative to a kidney transplant under the standard of care of tacrolimus.

[0011] The present disclosure also provides methods of inhibiting kidney transplant rejection in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the inhibiting kidney transplant rejection is relative to a control. In some embodiments, the control is a kidney transplant under the standard of care of tacrolimus. In some embodiments, the inhibiting of kidney transplant rejection is 10% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the inhibiting of kidney transplant rejection is 20% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the inhibiting of kidney transplant rejection is 30% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the inhibiting of kidney transplant rejection is 40% or more relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, the inhibiting of kidney transplant rejection is 50% or more relative to a kidney transplant under the standard of care of tacrolimus.

[0012] The present disclosure also provides methods of restoring kidney function in a subject having a kidney transplant, wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the restored kidney function is measured by an aggregate mean estimated glomerular filtration rate (eGFR). In some embodiments, kidney function is restored to an eGFR of greater than 50 mL/min/1.73 m^2. In some embodiments, kidney function is restored to an eGFR of greater than 60 mL/min/1.73 m^2. In some embodiments, kidney function is restored to an eGFR of greater than 70 mL/min/1.73 m^2. In some embodiments, kidney function is restored to an eGFR of greater than 80 mL/min/1.73 m^2. In some embodiments, kidney function is restored to an eGFR of greater than 90 mL/min/1.73 m^2. In some embodiments, kidney function is restored to a normal level following kidney transplant as measured by eGFR.

[0013] In some embodiments of the methods described herein, the subject is mammalian and/or human.

[0014] In some embodiments of the methods described herein, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 100 mg/kg. In some embodiments the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 50 mg/kg. In some embodiments the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 20 mg/kg. In some embodiments the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg. In some embodiments the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 20 mg/kg. In some embodiments the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 10 mg/kg.

[0015] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof is AT-1501.

[0016] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof comprises:

[0017] a heavy chain variable region (VH) comprising:

[0018] a CDR1 domain comprising the sequence set forth in SEQ ID NO: 9;

[0019] a CDR2 domain comprising the sequence set forth in SEQ ID NO: 74; and

[0020] a CDR3 domain comprising the sequence set forth in SEQ ID NO. 15, and

[0021] a light chain variable region (VL) comprising:

[0022] a CDR1 domain comprising the sequence set forth in SEQ ID NO: 72;

[0023] a CDR2 domain comprising the sequence set forth in SEQ ID NO: 73; and

[0024] a CDR3 domain comprising the sequence set forth in SEQ ID NO: 20.

[0025] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof comprises a light chain and a heavy chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence having at least 95% sequence identity with SEQ ID NO: 58, the heavy chain comprises a variable heavy chain region and an Fc region, wherein the heavy chain variable region comprises an amino acid sequence having at least 95% sequence identity with SEQ ID NO: 59, and the Fc region comprises the amino acid sequence set forth in SEQ ID NO: 60 or 61.

[0026] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 64 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 66. In some embodiments the heavy chain comprises the amino acid sequence of SEQ ID NO: 66 and an Fc region comprising the amino acid sequence of SEQ ID NO: 60 or 61.

[0027] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof is administered at least once every three weeks.

[0028] In some embodiments of the methods described herein the kidney transplant is a xenograft, allograft, or autograft.

[0029] In some embodiments of the methods described herein the subject suffers from a disease or disorder. In some embodiments the disease or disorder is an autoimmune disease, wherein the autoimmune disease is systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, or Graves' disease.

[0030] In some embodiments of the methods described herein the patient-to-donor HLA match is 4-6.

[0031] In some embodiments of the methods described herein the kidney is from a donor less than 60 years of age.

[0032] In some embodiments of the methods described herein the kidney is from a donor between 20-50 years of age.

[0033] In some embodiments of the methods described herein the subject is less than 70 years of age.

[0034] In some embodiments of the methods described herein the method further comprises administering one or more additional pharmaceutically effective compounds.

[0035] In some embodiments of the methods described herein the one or more additional compound blocks the interaction between CD28 and CD86 or between CD28 and CD80.

[0036] In some embodiments of the methods described herein the one or more additional compound targets at least one of the biomarkers selected from the group consisting of: interleukins, cytokines, and proinflammatory markers.

[0037] In some embodiments of the methods described herein the one or more additional compound is a CTLA4-Ig fusion protein, an abatacept, a belatacept, or a galiximab.

[0038] In some embodiments of the methods described herein the one or more additional pharmaceutically effective compounds includes anti-thymocyte globulin, mycophenolate mofetil or mycophenolate sodium, or prednisone or a prednisone equivalent.

[0039] In some embodiments of the methods described herein the one or more additional pharmaceutically effective compounds targets T-cells by one or more of clearing T-cells from circulation; or modulating T-cell activation, homing, or cytotoxic activities. In some embodiments the compound that targets T-cells is an anti-thymocyte globulin.

[0040] In some embodiments of the methods described herein the one or more additional pharmaceutically effective compounds inhibits inosine monophosphate dehydrogenase. In some embodiments of the methods described herein the compound that inhibits inosine monophosphate dehydrogenase is selected from a mycophenolate mofetil or a mycophenolate sodium.

[0041] In some embodiments of the methods described herein the one or more additional pharmaceutically effective compounds is a corticosteroid. In some embodiments the corticosteroid is selected from methylprednisolone, prednisolone,

prednisone, cortisone, hydrocortisone, betamethasone, dexamethasone, or triamcinolone. In some embodiments the corticosteroid is methylprednisolone or prednisolone.

[0042] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered on days 1, 3, 7, 14, 21, and 28 and every 21 days thereafter after transplant.

[0043] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered on days 1, 7, 14, 21, and 28 and every 21 days thereafter after transplant.

[0044] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof is administered parenterally or intravenously. In some embodiments the antibody or antigen binding fragment thereof is administered by injection or infusion. In some embodiments the antibody or antigen binding fragment thereof is administered by intravenous, intramuscular, or subcutaneous injection.

[0045] In some embodiments of the methods described herein the antibody or antigen binding fragment thereof is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] FIG. 1A shows MR1 concentration over time using a linear concentration (Y) axis.

[0047] FIG. 1B shows MR1 concentration over time using a log concentration (Y) axis.

[0048] FIG. 2 is a graph of the mean daily body weight measurements starting at day 40 to attainment of peak body weight for the control and the treatment group.

[0049] FIG. 3 depicts the mean daily body weight measurements from peak body weight to death for the control and treatment group.

[0050] FIG. 4 shows a Kaplan Meier Survival Plot for the control and treatment group as calculated by a Cox proportional hazard model.

[0051] FIG. 5A is a graph of the mean daily body weight measurements starting at day 40 to attainment of peak body weight for the control group and the MR1 treated group.

[0052] FIG. 5B is a graph depicting the mean daily body weight measurements from peak body weight to death for the control group and the MR1 treated group.

[0053] FIG. 5C shows the time to disease onset based on the time to progress to a neurological score of 2 in the control group and the MR1 treated group.

[0054] FIG. 5D shows the mean daily body weight measurements from peak body weight to death for the control and the MR1 treated group.

[0055] FIG. 6 is a graph showing the relative binding to human CD40L, of AT-1501 antibody (circles, dotted line), hu5c8 antibody (squares-solid line), and the control CTLA4-IgG1 (triangles).

[0056] FIG. 7A is a bar graph showing the ranked potency of 16 antibody clones versus the anti-CD40L antibody 5c8. Ranked potency is IC50 clone / IC50 of 5c8 x 100.

[0057] FIG. 7B is a bar graph showing the ranked potency of 16 antibody clones versus the anti-CD40L antibody AT-1501. Ranked potency is IC50 clone / IC50 of AT-1501 x 100.

[0058] FIGs. 8A-8G and 8I-8Q show the binding curves of the antibodies from each of the clones with the binding curve for 5c8. FIG. 8H shows thebinding curves of AT-1501 and 5c8.

[0059] FIGs. 9A-9G and 9I-9Q show the binding curves of the antibodies from each of the clones with the binding curve for AT-1501. FIG. 9H shows the binding curves of AT-1501 and 5c8.

[0060] FIGs. 10A and 10B are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRI. The only antibody having significant binding is the 5c8 antibody.

[0061] FIGs. 11A and 11B are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRIIa. The only antibody having significant binding is the 5c8 antibody.

[0062] FIGs. 12A and 12B are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRIIIa. None of the antibodies showed significant binding to FcγRIIIa.

[0063] FIGs. 12C and 12 D are graphs, each of which shows binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to FcγRIIIb. None of the antibodies showed significant binding to FcγRIIIb.

[0064] FIGs. 13A and 13B are graphs, each showing the binding of eight of the antibody clones, 5c8, AT-1501 and abatacept to C1q. The only antibody having significant binding to C1q was the 5c8 antibody.

[0065] FIGs. 14A-14D are graphs for the change in IgAN-associated proinflammatory markers in human subjects, 12 weeks after kidney transplants. An "*" represents data with a p value between 0.05 and 0.01; an "**" represents data with a p value between 0.01 and 0.001; an "***" represents data with a p value that is less than 0.001. The data plotted are for the IgAN-associated proinflammatory markers IgA (FIG. 14A), IgE (FIG. 14B), CD40L (FIG. 14C), and C3 (FIG. 14D).

[0066] FIGs. 15A-15D are graphs for the change in general transplant proinflammatory markers in human subjects, 12 weeks after kidney transplants. An "*" represents data with a p value between 0.05 and 0.01; an "**" represents data with a p value between 0.01 and 0.001; an "***" represents data with a p value that is less than 0.001. The data plotted are for the general transplant-associated proinflammatory markers CXCL9 (FIG. 15A), CXCL10 (FIG. 15B), IgM (FIG. 15C), and C3 (FIG. 15D).

[0067] FIG. 16 depicts a non-limiting example distribution of eGFR levels and cox proportional hazard model of graft loss across human participants, as discussed in Example 2.

[0068] FIG. 17 depicts a non-limiting cartoon schematic of the mechanistic overview of CD40L inflammatory signaling.

[0069] FIG. 18 depicts a graph of percent prevalence versus years after transplantation, and demonstrates that removing calcineurin inhibitors (CNIs) may stop the cycle of transplantation and subsequent CNI related graft failure.

[0070] FIG. 19 depicts the distribution of eGFRs using standard of care post transplant, wherein the median eGFR is about 51 mL/min/1.73 m^2 in the first year.

[0071] FIG. 20 depicts the demographics and disposition of 13 human subject participants for a Phase 1b Kidney Transplantation study, as discussed in Example 2 below.

[0072] FIG. 21 depicts the adverse effects following treatment during a Phase 1b Kidney Transplantation study.

[0073] FIGs. 22A-22B depict the mean eGFR over time in all patients (FIG. 22A) and excluding a subject with a surgical complication unrelated to administration of tegoprubart at day 0 (FIG. 22B) during a Phase 1b Kidney Transplantation study,

calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. N is the number of participants at that time contributing data to mean eGFR calculation.

[0074] FIG. 23 depicts a non-limiting cartoon graphic of the experiment methodology for a Phase 1b Kidney Transplantation study.

[0075] FIG. 24 depicts the survival probability versus time in non-human primates (NHP) post kidney transplant for a variety of therapies. The graph represents aggregated data from published studies. Meta-analysis not based on head-to-head studies. Differences between any individual programs may vary.

[0076] FIG. 25 depicts the eGFR over time for individual patients during a Phase 1b Kidney Transplantation study. Calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation. N is the number of participants at that time contributing data to mean eGFR calculation. In light gray is the mean value of eGFR concentration in patients given Tac (tacrolimus) prior to kidney transplantation.

[0077] FIG. 26 depicts the relative expression levels of CD40 Ligand and CD40 Receptor across a variety of human tissue types, as assessed using scRNA-seq.

[0078] FIG. 27 depicts the mean eGFR over time in all patients during a Phase 1b Kidney Transplantation study, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. N is the number of participants at that time contributing data to mean eGFR calculation.

DETAILED DESCRIPTION

[0079] As described herein, the present disclosure provides methods of kidney transplant graft survival. For example, the present disclosure provides methods of improving transplanted kidney function in a subject in need thereof, where the transplanted kidney function is measured by an aggregate mean estimated glomerular filtration rate (eGFR) and is improved relative to a control, such as standard of care of tacrolimus. The present disclosure also provides methods of restoring kidney function in a subject having a kidney transplant, where the restored kidney function is measured by an aggregate mean estimated glomerular filtration rate (eGFR). According to the methods described herein, where the methods comprise administering to subjects in

need thereof a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand as described herein, the methods surprisingly support kidney transplant survival and prevent rejection of a transplanted kidney as measured by eGFR of greater than 60 mL/min/1.73 m^2 for periods of at least 30 days, 90 days, or a year or more following transplant.

[0080] In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the present disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein. All references cited herein are expressly incorporated by reference herein in their entirety and for the specific disclosure referenced herein.

Definitions

[0081] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications referenced herein are incorporated by reference in their entirety unless stated otherwise. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0082] One of ordinary skill in the art will appreciate that starting materials, biological and chemical materials, biological and chemical reagents, synthetic methods, purification methods, analytical methods, assay methods, and biological methods other than those specifically exemplified can be employed in the practice of the disclosure without resort to undue experimentation. All art-known functional equivalents, of any such materials and methods are intended to be included in this disclosure.

[0083] As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. The terms “a” (or “an”), as well as the terms “one or more,” and “at least one” can be used interchangeably herein. In certain

aspects, the term “a” or “an” means “single.” In other aspects, the term “a” or “an” includes “two or more” or “multiple.”

[0084] Furthermore, “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0085] The use of the conjunction “or” is used interchangeably with at “least one of.” For example: where a composition comprises A or B, the method must comprise at least one of A and B but may also comprise both A and B. Likewise a composition comprising “A, B, C or D” must comprise at least one of the group of A, B, C and D, but may also comprise all or any combination of A, B, C and D.

[0086] As used herein, the term “about” or “approximately” has its usual meaning as understood by those skilled in the art and thus indicates that a value includes the inherent variation of error for the method being employed to determine a value, or the variation that exists among multiple determinations. In certain aspects, variations may include ±20%, ±10%, ±5%, ±l%, or ±0.1 % from the specified value.

[0087] Amino acid substitutions are denoted by the convention in which the original amino acid, the position of the amino acid in the specified sequence and the replacement amino acid are identified, for example, C11S would indicate that the cysteine at position 11 of the polypeptide sequence is replaced with a serine.

[0088] Humanized antibodies are antibodies produced from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans. The process of “humanization” is usually applied to monoclonal antibodies developed for administration to humans (for example, antibodies developed as anti- cancer drugs).

[0089] Currently it is common to humanize a non-human antibody by insertion of relevant CDRs from antibodies created in a non-human animal into a human antibody “scaffold”. “Direct” creation of a humanized antibody can be accomplished by inserting the appropriate CDR coding segments (responsible for the desired binding properties) into a human antibody “scaffold.” This may be achieved through

recombinant DNA methods using an appropriate vector and expression in mammalian cells. That is, after an antibody is developed to have the desired properties in a mouse (or other non-human), the DNA coding for that antibody can be isolated, cloned into a vector and sequenced. The DNA sequence corresponding to the antibody CDRs can then be determined. Once the precise sequence of the desired CDRs is known, a strategy can be devised for inserting these sequences appropriately into a construct containing the DNA for a human antibody variant. The CDRs may also be varied, e.g., to increase specificity, prior to insertion into the scaffold.

[0090] The term human antibody refers to an antibody which possesses an amino acid sequence which corresponds to that of an antibody produced by a human and/or has been made using any technique for making human antibodies. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen binding residues.

[0091] The term "variant" as used herein is defined as a modified or altered form of a wildtype sequence, e.g., where one or more amino acids may be replaced by other amino acid(s) or non-amino acid(s) which do not substantially affect function. In some embodiments, the variant may contain an altered side chain for at least one amino acid residue.

[0092] The term "antigen" as used herein is defined as an entity that can stimulate the production of antibodies and specifically combine with them and/or an entity which elicits an immune system response. For example, a cell surface protein or a specific linear or non- linear portion thereof. The term herein may be abbreviated to "Ag."

[0093] An "antigen binding antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fd fragments, dAb fragments, Fab'-SH, F(ab')2; diabodies; triabodies; linear antibodies; single-chain antibody molecules (e.g., scFv); and multispecific antibodies formed from antibody fragments, 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). An antigen binding fragment as disclosed in the present application binds to the antigen CD40L.

[0094] 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 VH domain associated with a VL domain, the VH and VL domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain VH-VH, VH-VL or VL-VL dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric VH or VL domain.

[0095] The isolated antibody includes bispecific antibodies in which each arm of the antibody or the antigen binding fragment binds to a different target or epitope.

[0096] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region.

[0097] "5c8" refers to the mouse anti-human antibody that binds CD40L and is produced by the hybridoma that is available from the ATCC having the accession number HB10916 and is described in U.S. Pat. No. 5,474,771. "hu5c8" refers to a humanized version of 5c8 the sequence of which is disclosed in Karpusas, et al., Structure vol. 9, pp 321-329, (2001).

[0098] 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 physiological conditions. Specific binding may be characterized by an equilibrium dissociation constant (KD) of about 3000 nM or less (i.e., a smaller KD denotes a tighter binding), about 2000 nM or less, about 1000 nM or less; about 500 nM or less; about 300 nM or less; about 200 nM or less; about 100 nM or less; about 50 nM or less; about 1 nM or less; or about 0.5 nM. Specific binding for a particular antigen or an epitope may be exhibited, for example, by an antibody having a KD for an antigen or epitope of at least about 1×10^{-4} M, at least about 1×10^{-5} M, at least about 1×10^{-6} M, at least about 1×10^{-7} M, at least about 1×10^{-8} M, at least about 1×10^{-9} M, alternatively at least about 1×10^{-10} M, at least about 1×10^{-11} M, at least about 1×10^{-12} M, or greater, where KD refers to a equilibrium dissociation constant of a particular antibody-antigen interaction. Typically, an antibody that specifically binds an antigen will have a KD that is 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for a control molecule relative to the antigen or epitope. Also, specific binding

for a particular antigen or an epitope may be exhibited, for example, by an antibody having a Ka for an antigen or epitope of at least 20-, 50-, 100-, 500-, 1000-, 5,000, 10,000- or more times greater for the epitope relative to a control, where Ka refers to an association rate of a particular antibody- antigen interaction.

[0099] The term "neutralizing antibody" includes an antibody that is capable of inhibiting and/or neutralizing the biological activity of CD40L, for example an anti-CD40L antibody or antigen fragment thereof that inhibits or prevents or diminishes the binding of CD40L to CD40, and thus inhibiting or reducing the signaling pathway triggered by CD40L and/or inhibiting or reducing the binding of CD40L to CD40.

[0100] The terms "antagonistic antibody" or "antagonist antibody" are used herein equivalently and include an antibody that is capable of inhibiting and/or neutralizing the biological signaling activity of CD40L, as described for a neutralizing antibody *supra*.

[0101] The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the methods and compositions disclosed herein. Thus, it should be understood that although aspects of the present disclosure have been specifically disclosed by various embodiments which may include preferred embodiments, exemplary embodiments and optional features, modifications and variations of the concepts herein disclosed may be resorted to by those skilled in the art. Such modifications and variations are considered to be within the scope of embodiments of the disclosure as described and as may be defined by the appended claims.

[0102] Reference in the specification is made to percent identity between polypeptide or amino acid sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. Identity can be measured as "local identity" or "global identity." Local identity refers the degree of sequence relatedness between polypeptides as determined by the match between strings of such sequences. Global identity refers to the degree of sequence relatedness of a polypeptide compared to the full-length of a reference polypeptide. Unless specified otherwise, as used herein,

identity means global identity. For the purposes of this disclosure, the percentages for global identity are calculated using Needleman and Wunsch ((1970) J. Mol. Biol. 48:444-453) algorithm using a Blossum 62 scoring matrix with a gap penalty of 12, a gap extend penalty of 4, and a frameshift gap penalty of 5. There are many publicly available software programs that incorporate the Needleman and Wunsch algorithm, e.g., the GAP program in the GCG software package.

[0103] CD40L is also known as CD154, gp39, T-BAM, 5c8 antigen, or TNF related activation protein (TRAP).

[0104] Throughout this specification, unless the context requires otherwise, the words "comprise," "comprises," and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present depending upon whether or not they materially affect the activity or action of the listed elements.

[0105] The terms "function" and "functional" as used herein have their plain and ordinary meaning as understood in light of the specification, and refer to a biological, enzymatic, or therapeutic function.

[0106] The term "yield" of any given substance, compound, or material as used herein has its plain and ordinary meaning as understood in light of the specification and refers to the actual overall amount of the substance, compound, or material relative to the expected overall amount. For example, the yield of the substance, compound, or material is, is about, is at least, is at least about, is not more than, or is not more than about, 80, 81, 82, 83, 84, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% of the expected overall amount, including all decimals in between. Yield may be affected by the efficiency of a reaction or process, unwanted side reactions, degradation, quality of

the input substances, compounds, or materials, or loss of the desired substance, compound, or material during any step of the production.

[0107] As used herein, the term "isolated" has its plain and ordinary meaning as understood in light of the specification, and refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from equal to, about, at least, at least about, not more than, or not more than about, 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, substantially 100%, or 100% of the other components with which they were initially associated (or ranges including and/or spanning the aforementioned values). In some embodiments, isolated agents are, are about, are at least, are at least about, are not more than, or are not more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, substantially 100%, or 100% pure (or ranges including and/or spanning the aforementioned values). As used herein, a substance that is "isolated" may be "pure" (e.g., substantially free of other components). As used herein, the term "isolated cell" may refer to a cell not contained in a multi-cellular organism or tissue.

[0108] The term "isolated protein" or "isolated polypeptide" (e.g., an isolated antibody or isolated antigen binding fragment) is a protein or polypeptide that by virtue of its origin or source of derivation is not associated with naturally associated components that accompany it in its native state; is substantially free of other proteins from the same species; is expressed by a cell from a different species; or does not occur in nature. Thus, a polypeptide that is chemically synthesized or synthesized in a cellular system different from the cell from which it naturally originates will be "isolated" from its naturally associated components. A protein may also be rendered substantially free of naturally associated components by isolation, using protein purification techniques well known in the art.

[0109] As used herein, "in vivo" is given its plain and ordinary meaning as understood in light of the specification and refers to the performance of a method inside living organisms, usually animals, mammals, including humans, and plants, or living cells which make up these living organisms, as opposed to a tissue extract or dead organism.

[0110] As used herein, “ex vivo” is given its plain and ordinary meaning as understood in light of the specification and refers to the performance of a method outside a living organism with little alteration of natural conditions.

[0111] As used herein, “in vitro” is given its plain and ordinary meaning as understood in light of the specification and refers to the performance of a method outside of biological conditions, e.g., in a petri dish or test tube.

[0112] As used herein, “nucleic acid”, “nucleic acid molecule”, or “nucleotide” refers to polynucleotides or oligonucleotides such as deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), oligonucleotides, fragments generated by the polymerase chain reaction (PCR), and fragments generated by any of ligation, scission, endonuclease action, exonuclease action, and by synthetic generation. Nucleic acid molecules can be composed of monomers that are naturally occurring nucleotides (such as DNA and RNA), or analogs of naturally occurring nucleotides (e.g., enantiomeric forms of naturally occurring nucleotides), or a combination of both. Modified nucleotides can have alterations in sugar moieties and/or in pyrimidine or purine base moieties. Sugar modifications include, for example, replacement of one or more hydroxyl groups with halogens, alkyl groups, amines, and azido groups, or sugars can be functionalized as ethers or esters. Moreover, the entire sugar moiety can be replaced with sterically and electronically similar structures, such as aza-sugars and carbocyclic sugar analogs. Examples of modifications in a base moiety include alkylated purines and pyrimidines, acylated purines or pyrimidines, or other well-known heterocyclic substitutes. Nucleic acid monomers can be linked by phosphodiester bonds or analogs of such linkages. Analogs of phosphodiester linkages include phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranilidate, phosphoramidate, and the like. The term “nucleic acid molecule” also includes so-called “peptide nucleic acids,” which comprise naturally occurring or modified nucleic acid bases attached to a polyamide backbone. Nucleic acids can be either single stranded or double stranded.

[0113] The terms “peptide”, “polypeptide”, and “protein” as used herein have their plain and ordinary meaning as understood in light of the specification and refer to macromolecules comprised of amino acids linked by peptide bonds. The numerous functions of peptides, polypeptides, and proteins are known in the art, and include but are not limited to enzymes, structure, transport, defense, hormones, or signaling.

Peptides, polypeptides, and proteins are often, but not always, produced biologically by a ribosomal complex using a nucleic acid template, although chemical syntheses are also available. By manipulating the nucleic acid template, peptide, polypeptide, and protein mutations such as substitutions, deletions, truncations, additions, duplications, or fusions of more than one peptide, polypeptide, or protein can be performed. These fusions of more than one peptide, polypeptide, or protein can be joined in the same molecule adjacently, or with extra amino acids in between, e.g. linkers, repeats, epitopes, or tags, or any other sequence that is, is about, is at least, is at least about, is not more than, or is not more than about, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 150, 200, or 300 bases long, or any length in a range defined by any two of the aforementioned lengths. The term "downstream" on a polypeptide as used herein has its plain and ordinary meaning as understood in light of the specification and refers to a sequence being after the C- terminus of a previous sequence. The term "upstream" on a polypeptide as used herein has its plain and ordinary meaning as understood in light of the specification and refers to a sequence being before the N-terminus of a subsequent sequence.

[0114] The term "gene" as used herein have their plain and ordinary meaning as understood in light of the specification, and generally refers to a portion of a nucleic acid that encodes a protein or functional RNA; however, the term may optionally encompass regulatory sequences. It will be appreciated by those of ordinary skill in the art that the term "gene" may include gene regulatory sequences (e.g., promoters, enhancers, etc.) and/or intron sequences. It will further be appreciated that definitions of gene include references to nucleic acids that do not encode proteins but rather encode functional RNA molecules such as tRNAs and miRNAs. In some cases, the gene includes regulatory sequences involved in transcription, or message production or composition. In other embodiments, the gene comprises transcribed sequences that encode for a protein, polypeptide, or peptide. In keeping with the terminology described herein, an "isolated gene" may comprise transcribed nucleic acid(s), regulatory sequences, coding sequences, or the like, isolated substantially away from other such sequences, such as other naturally occurring genes, regulatory sequences, polypeptide, or peptide encoding sequences, etc. In this respect, the term "gene" is used for simplicity to refer to a nucleic acid comprising a nucleotide sequence that is

transcribed, and the complement thereof. As will be understood by those in the art, this functional term "gene" includes both genomic sequences, RNA or cDNA sequences, or smaller engineered nucleic acid segments, including nucleic acid segments of a non-transcribed part of a gene, including but not limited to the non-transcribed promoter or enhancer regions of a gene. Smaller engineered gene nucleic acid segments may express or may be adapted to express using nucleic acid manipulation technology, proteins, polypeptides, domains, peptides, fusion proteins, mutants and/or such like.

[0115] The terms "individual", "subject", "host," or "patient" as used herein have their usual meaning as understood by those skilled in the art and thus includes a human or a non-human mammal. The term "mammal" is used in its usual biological sense. Thus, it specifically includes, but is not limited to, primates, including simians (chimpanzees, apes, monkeys), humans, cattle, horses, sheep, goats, swine, rabbits, dogs, cats, rodents, rats, mice, or guinea pigs.

[0116] The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dimension is intended to mean both the recited value and a functionally equivalent range surrounding that value. For example, a dimension disclosed as "20 mm" is intended to mean "about 20 mm".

[0117] The following abbreviations are used herein: super oxide dismutases-1 (*SOD1*); T cell receptor (TCR); major histocompatibility complex (MHC) antigen presenting cell (APC); Phosphate buffered saline (PBS), complementarity determining regions (CDR). "IP" means intraperitoneally and "IV" means intravenously.

[0118] MR1 is a hamster monoclonal antibody that binds to mouse CD40 ligand. "Wild type" as used herein means a non-transgenic mouse.

[0119] As used herein "small molecule" means a compound having a molecular weight of less than 2000 Daltons.

[0120] The terms "treating," "treatment," or "therapy," as used herein includes prophylactic and therapeutic treatment and refer to any indicia of success in arresting or ameliorating a transplant rejection in a subject, including partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of, reducing severity of, reducing incidence of, or attenuating one or more of the symptoms associated with a transplant rejection, or any combination thereof.

[0121] The phrase "therapeutically effective amount" means an amount of a compound such as an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, that is needed to produce the desired therapeutic effect, which for the present disclosure is an amount sufficient to inhibit, or allow an improvement in the disorder or condition being treated (including treatment or prevention of transplant rejection) when administered alone or in conjunction with another pharmaceutical agent or treatment in a particular subject or subject population.

[0122] As used herein, the term "improve" has its ordinary meaning as understood in light of the specification, and may not refer to a 100% or complete improvement. Rather, there are varying degrees of improvement of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In exemplary embodiments, the improvement provided by the methods of the present disclosure is at least or about a 10% improvement (e.g., at least or about a 20% improvement, at least or about a 30% improvement, at least or about a 40% improvement, at least or about a 50% improvement, at least or about a 60% improvement, at least or about a 70% improvement, at least or about a 80% improvement, at least or about a 90% improvement, at least or about a 95% improvement, at least or about a 98% improvement) relative to a control. As used herein, the term "control" with respect to comparison of improvement of transplant has its ordinary meaning as understood in light of the specification and may refer to a standard of care, treatment without the compositions described herein, or prior measured time points. In some embodiments, an improvement in transplant function is relative to a transplant under standard of care. For example, an improvement in kidney transplant is relative to a kidney transplant under the standard of care of tacrolimus. In some embodiments, an improvement in kidney transplant is relative to a kidney transplant under the standard of care of a mammalian target of rapamycin (mTOR) inhibitor such as sirolimus or everolimus. In some embodiments, an improvement in kidney transplant is relative to a kidney transplant under the standard of care of azathioprine. In some embodiments, an improvement in kidney transplant is relative to a kidney transplant under the standard of care of cyclosporine. In some embodiments, an improvement in kidney transplant is relative to a kidney transplant under the standard of care of belatacept. In some embodiments, an improvement in transplant function is relative to treatment without the compositions described herein. In some embodiments, an improvement in

transplant function is relative to prior measured function of the transplant, wherein the improvement takes place over time relative to prior measured function. Additional controls are known to those of skill in the art and may be used as a standard for measuring improvement in transplant function.

[0123] As used herein, the term "inhibit" refers to the reduction or prevention of a transplant rejection, such as a kidney transplant rejection. The reduction can be by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100%, or an amount that is within a range defined by any two of the aforementioned values. As used herein, the term "delay" refers to a slowing, postponement, or deferment of an event, such as a transplant rejection, such as a kidney transplant rejection, to a time which is later than would otherwise be expected. The delay can be a delay of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or an amount within a range defined by any two of the aforementioned values. The terms inhibit and delay are not to be construed as necessarily indicating a 100% inhibition or delay. A partial inhibition or delay may be realized.

[0124] An "effective amount" of an agent, e.g., a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0125] "Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y may generally be represented by the equilibrium dissociation constant (KD), a ratio of k_{off}/k_{on}, between the antibody and its antigen. KD and affinity are inversely related. The KD value relates to the concentration of antibody (the amount of antibody needed for a particular experiment) and so the lower the KD value (lower concentration) and thus the higher the affinity of the antibody. Affinity may be measured by common methods known in the art, including those described herein. Specific, illustrative, and exemplary embodiments for measuring binding affinity may be measured by radioimmunoassays (RIA), Surface Plasmon Resonance (SPR) on a BIAcore® instrument (GE Healthcare Europe GmbH, Glattbrugg, Switzerland) by capturing the antibody on a protein-A coupled CM5 research grade sensor chip (GE Healthcare Europe GmbH, Glattbrugg,

Switzerland; BR-1000-14) with a human CD40 ligand polypeptide used as analyte. Other methods may include radioimmunoassays, and the Kinetic Exclusion Assay. The Kinetic Exclusion Assay is a general-purpose immunoassay platform that is capable of measuring equilibrium dissociation constants, and association and dissociation rate constants for antigen/anti-body interactions.

[0126] TMB is an abbreviation of 3,3′,5,5′-Tetramethylbenzidine.

[0127] "CDR domain" as used herein means an antibody complementary determining region with or without flanking sequences.

[0128] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation. One effector function is ability of the Fc or constant region of an antibody to bind proteins including, but not limited to, an Fc receptor (FcR) (e.g., high affinity Fc region of IgG receptor Ia (FCγRIa) (CD64), low affinity immunoglobulin gamma Fc region acceptor IIa (FCγRIIa) (CD32), low affinity immunoglobulin gamma Fc region receptor IIIa (FCγRIIIA) (CD16a), low affinity immunoglobulin gamma Fc region receptor IIIb (FCγRIIIb) (CD16b)). In some embodiments, where the antibodies and antigen binding fragments thereof, have an Fc domain, the Fc domain has been engineered to reduce or eliminate one or more Fc effector function. In a preferred embodiment the Fc domain has been engineered to reduce or eliminate platelet activation and/or platelet aggregation and the concomitant risk of thromboembolism.

CD40L Inhibition and Immunosuppression in Transplant Generally and in Animal Models

[0129] The co-stimulatory pathway involves, along with other interactions, the binding of CD40 on B cells to CD40L (also known as CD154, gp39, T-BAM, 5c8 antigen, CD40CR and TRAP) on T cells. The human CD40 and CD40 Ligand (CD40L) are differentially expressed throughout tissues (FIG. 26). While mRNA levels of human CD40L are relatively higher in T cells, mRNA levels of human CD40 are higher in B cells and myeloid cell lineages. Human CD40 is expressed on mature B cells, as well as macrophages, dendritic cells, fibroblasts and activated endothelial cells. It is thought

that blockade of the CD40:CD40L binding promotes the development of Type I T-helper cell responses.

[0130] Using compounds that block these interactions and inhibit the co-stimulatory signals, a significant body of work has demonstrated the immunomodulatory effects of blocking one or more of CD40L, CD80 or CD86 in preclinical models of transplantation and autoimmunity. Blocking CD40L function with blocking antibodies or adenoviral expression of CD40L-Ig improves allograft transplant by 30 to 90 days. Similar studies blocking CD80/CD86 on APCs with CTLA4-Ig or adenoviral expression of CTLA4- Ig transiently improves allograft transplant survival. Transplant rejection in these models is transient and graft rejection ensues over time. Longer term repression of transplant rejection can be accomplished by blocking both the co-stimulatory pathway with CTLA4-Ig and blocking CD40L activation of APCs with anti-CD40L antibodies.

[0131] Blocking antibodies to CD40L or genetic deletion of CD40L in mice has demonstrated that CD40L ameliorates disease progression, survival, and surrogate markers of disease in preclinical models of experimental allergic encephalomyelitis (EAE) a model of multiple sclerosis, collagen induced arthritis, and systemic lupus. Blockade of CD40:CD40L binding appears to reduce the ability of macrophages to produce nitric oxide, which mediates many of the macrophages' pro-inflammatory activities.

[0132] It appears from such studies that blocking CD40:CD40L interactions and/or blocking of CD28:CD80 or CD28:CD86 interactions can modulate immune responses. Interaction of CD40 with CD40L on immune cells mediates activation of the co-stimulatory immune pathway, controlling cross talk between the adaptive and innate immune systems. Maximal activation of inflammatory system is a 3-step process, requiring co-stimulatory signaling, including: step 1, major histocompatibility complexes (MHC) and CD3/TCR engagement; step 2, CD40 and CD40L binding resulting in cell division and clonal expansion; and step 3, pro-inflammatory response by polarized T cells expressing inflammatory chemokines and cytokines. Blocking CD40L shifts polarization away from pro-inflammatory signaling to T cell anergy, apoptosis, and polarization to a Treg environment. Blocking CD40L thus does not generally result in lymphopenia often seen with immunosuppressive agents (FIG. 17).

[0133] Removing calcineurin inhibitors (CNIs) may stop the cycle of transplantation and subsequent CNI related graft failure (FIG. 18). CNI side effects are a leading cause of kidney graft failure over time, and can lead to a cycle of transplantation and graft failure, that includes: CNI associated kidney damage, including nephrotoxicity, hypertension, and diabetes; graft failure, resulting in increased medical costs and burden; dialysis and kidney wait lists, where about 15% of adults on waitlists are for repeat transplants and about 15-20% mortality rate in the first year of dialysis; and transplant, resulting in enormous cost per patient.

[0134] Immunohistochemical data was shown to correlate well with the gene expression data and these data identify macrophages as an antigen-presenting cell infiltrating skeletal muscle during disease progression in the G93A mouse.

[0135] In order to determine the presence and localization of potential antigen-presenting cells in gastrocnemius muscle from G93A and wild type animals, immunohistochemistry was performed on gastrocnemius tissues that were harvested from G93A and wildtype mice, at day 110. Immediately after harvesting, the tissues were embedded in OCT. Frozen sections were H&E stained and hybridized with antibodies to myelin (anti-S100b antibody) or antibodies to hematopoietic cell lineages including T cells (anti-CD3 antibody), B cells (CD45R pan B cell antibody), and macrophages (anti-CD11b antibody). At day 110, infiltration of CD11b positive macrophages was present, and the macrophages appeared to be localized to the axons of nerves innervating the skeletal muscle. The localization of macrophages was not dispersed across the entire muscle, suggesting that the inflammation was not due to muscle atrophy or muscle fiber remodeling.

[0136] In order to confirm the identity of the monocyte lineage cells in the skeletal muscle at day 110 and to clarify the relevance of these cells compared to non-transgenic animals, additional immunohistochemistry was performed with a panel of antibodies specific for the macrophage lineage. An anti-S100b antibody was utilized to label the myelin associated axons innervating the skeletal muscle. All of the macrophage specific antibodies (anti-CD11b antibody, anti-CD86 antibody and anti-MAC1antibody) localized macrophages to the axons of nerves innervating the skeletal muscle of G93A mice with no macrophages present on the axons of wildtype animals. The localization of macrophages was specific for nerves innervating the muscle with no macrophages present on myofibers in the muscle.

[0137] The gene expression data suggest that the genes associated with the co-stimulatory pathway are temporally increasing during disease progression both in spinal cord as well as in skeletal muscle. In order to characterize the timing of macrophage infiltration into skeletal muscle immunohistochemistry was performed on gastrocnemius sections from days 60, 80, and 100 in G93A mice. There was no evidence of macrophage infiltration and localization to axons at day 60. Macrophages were evident at day 80 and localized to the axons innervating the muscle as described previously for skeletal muscle at day 110. The number of macrophages increased between day 80 and day 100 and accumulation of macrophages was specific to the axons innervating the skeletal muscle.

[0138] In order to quantitate the increase in macrophage infiltration, representative sections from 5 G93A and 5 wild type animals were hybridized with anti-CD86 antibody and the number of macrophages per 10,000 square microns were counted. The number of macrophages in the wild type animals was the same at the 60-, 80- and 110-day time points. Macrophages accumulate in skeletal muscle temporally between days 80 and 100 and there are very few macrophages present in wild type skeletal muscle.

[0139] In summary, the immunohistochemical data correlate very well with the gene expression data and identify macrophages as the antigen-presenting cell infiltrating skeletal muscle during disease progression in the G93A mouse model. An unexpected finding is that the macrophage infiltration appears to be specifically targeted to the axons innervating the skeletal muscle as localized by labeling with antibodies to myelin and macrophages.

[0140] Tissue levels of MR1 directed against murine CD40L were determined using a matrix matched, non-competitive enzyme linked immunosorbent assay (ELISA) in the sandwich format. Seven-point standard curves were included on each plate. Standards were prepared using purified MR1 spiked into PBS diluent solution. PBS diluent solution was matrix matched with the normal mouse tissue at the equivalent dilution of the unknown samples to correct for any non-specific effects resulting from tissue lysates.

[0141] 84 plasma samples were taken for pharmacokinetic analysis over a period of two weeks after dosing (10 mg/kg, IP) in both female and male G93A mice.

[0142] The elimination half-life was similar in females (23 days) and males (22 days) and similar to the half-life for a typical mouse IgG2-based antibody in the mouse. No signs of anti- hamster antibody response were seen.

[0143] Females show a somewhat smaller volume of distribution for MR1 than males, and thus show higher plasma levels when given the same 10 mg/kg dose. Males show a faster clearance and higher volume of distribution. Thus, to attain similar plasma levels, males would require a higher dose. FIG. 1A shows MR1 concentration over time using a linear concentration (Y) axis. FIG. 1B shows MR1 concentration over time using a log concentration (Y) axis.

[0144] 36 female G93A mice were litter matched and randomized into two study groups. 18 G93A mice were placed into the MR1-treatment group and the other 18 G93A mice were placed into the control group. Study days are based on days from birth.

[0145] A single injection of 56 µg of MR1 was administered intraperitoneally (IP) on day 50. Subsequent to the bolus injection, a weekly maintenance injection of 18 µg of MR1 was administered by IP injection. Doses were prepared in vehicle (phosphate buffered saline (PBS, pH 7.3)), to a total volume 200 µl. Control animals where administered 200 µl PBS. Beginning at day 54, animals were monitored daily throughout the course of the study and daily body weight measurements were taken.

[0146] Mutant SOD1 transgenic animals display normal body weight (BW) characteristics as neonates and gain weight normally compared to non-transgenic animals into adulthood. Depending on the nature of the genetic mutation in the transgene and the number of copies of mutant transgene weight loss becomes apparent in adult animals and continues until death. Analysis of weight loss in treatment and control groups can provide insight into putative treatment effects on disease onset and rate of progression. In order to assess the impact of MR1 treatment on body weight, two summary parameters are examined: (1) changes in BW from initiation of study to the attainment of peak body weight which may reflect an impact on disease onset; and (2) the changes in BW from peak body weight until death which may reflectan impact on disease progression.

[0147] Comparative MR1-treated and control group time-to-event curves for the time from day 40 to the attainment of peak body weight are shown in FIG. 2. The median time to peak body weight for the control group was 50 days compared to the MR1 treated group, which was 51 days. This difference was not significant when analyzed by Kaplan Meier using the log rank and Wilcoxon statistical models, Cox proportional hazard, or parametric statistical tests.

[0148] Comparative MR1-treated and control group time-to-event curves for the time from peak body weight to death are shown in FIG. 3. Time from peak body weight to death was statistically significantly later by 15 days in MRI treated animals. Control animals have a 2.4 to 4.7-fold greater risk of dying sooner after attaining peak body weight than did MR1-treated animals. The median time from peak body weight to death in the control group was 26 days whereas in the MR1 treated group it was 41 days. Significance for each of the analyses in this example was calculated in several ways in order to better evaluate significance. The delay is statistically significant when analyzed using several approaches. (Kaplan Meier, log rank p=0.0110 and Wilcoxon, p=0.0069; Cox proportional Hazard model p=0.05151; parametric statistical model, p=0.0122). Based on the body weight data, MR1 appears to have less of an impact on the onset of disease in the G93A mouse model but has a dramatic effect in slowing down the rate of body weight loss from peak body weight until death.

[0149] Treated animals survival time was later by 13 days than control animals. Comparative MR1-treated and control group time-to-event curves for the time from peak body weight to death are shown in FIG. 4. The median survival time for the control group was 128 days and the median survival for the MR1 treated group was 141 days. Control animals had a 2.8 to 3.2-fold greater risk of dying sooner than did MR1 treated animals. The delay is statistically significant when analyzed using several approaches. (Kaplan Meier, log rank (p= 0.0040) and Wilcoxon test (p = 0.0109); Cox proportional hazard model (p = 0.0060); parametric analysis, (p = 0.0049)). 60 female and 36 male G93A mice were litter matched and randomly assigned to treatment or control groups. 30 of the female and 18 of the male mice were treated with MR1 starting at day 50. Study days are based on birth.

[0150] A single bolus injection of 5.22 mg/kg or 6.75 mg/kg of MR1 was administered intraperitoneally at day 50 in females or males, respectively. Subsequent to the bolus injection, females received weekly injections of 1 mg/kg of MR1, and males received weekly injections of 1.34 mg/kg of MR1 via IP injection. Doses were prepared in vehicle (phosphate buffered saline (PBS, pH 7.3)), to a total volume of 200µl. Control animals where administered 200µl PBS. Animals were monitored for body weight, and criteria for euthanization as previously described.

[0151] Comparative MR1-treated and control group time-to-event curves for the time from day 40 to the attainment of peak body weight are shown in FIG. 5A. The median

time to peak body weight for the control group was 49 days compared to the MR1 treated group, which was 53 days. This difference was not significant when analyzed by Kaplan Meier using the log rank and Wilcoxon statistical models, Cox proportional hazard, or parametric statistical tests.

[0152] Comparative MR1-treated and control group time-to-event curves for the time from peak body weight to death are shown in FIG. 5B. Time from peak body weight to death was statistically significantly later by 6 days in MRI treated animals. The median time from peak body weight to death in the control group was 29 days whereas in the MR1 treated group it was 35 days. Significance for each of the analyses in this example was calculated in several ways in order to better evaluate significance. The delay is statistically significant when analyzed using several statistical models: Kaplan Meier, log rank ($p=0.0413$) and Wilcoxon, ($p=0.0732$); and the Cox proportional Hazard model ($p=0.0460$). Based on the body weight data, MR1 appears to have less of an impact on the onset of disease in the G93A mouse model but has a dramatic effect in slowing down the rate of body weight loss from peak body weight until death.

[0153] The time-to-event plots for the age at which MR1 and control group animals progressed to a neurological score of 2 and the number of days at a neurological score of 2 is shown in FIG. 5C. The time to attain a score of 2 in the control group was 113 days and for the MR1 treated group is 121 days. Based on the neurological score data, MR1 delays disease onset in the G93A mouse model by approximately 8 days and the delay is statistically significant when analyzed using several statistical models: Kaplan Meier, log rank ($p = 0.0038$) and Wilcoxon; ($p = 0.0017$); and the Cox proportional hazard model, ($p = 0.0010$).

[0154] Treated animals survival time was later by 9 days than control animals. The median survival time for the control group was 124 days and the median survival for the MR1 treated group was 133 days, as shown in FIG. 5D. The delay is statistically significant when analyzed using several statistical models: Kaplan Meier, log rank ($p = 0.0043$) and Wilcoxon test ($p = 0.0040$); and the Cox proportional hazard model ($p = 0.0030$).

[0155] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

[0156] Nucleic acid sequences encoding the heavy chain and the light chain of the desired antibody were designed to be suitable for expression in mammalian cells such as Chinese Hamster Ovary (CHO) cells. The nucleic acids were then artificially synthesized and ligated into the antibody expression vector BPJPuro using standard molecular biology techniques. BPJPuro is a dual gene mammalian expression vector optimized for selectable and stable expression of immunoglobulins in Chinese Hamster Ovary (CHO) cells. The vector was then transfected into CHO cells and stable transfectants selected.

[0157] Similarly, a nucleic acid (SEQ ID NO: 67) encoding a heavy chain having the amino acid sequence of SEQ ID NO: 66, and a nucleic acid (SEQ ID NO: 65) encoding a light chain having the amino acid sequence of SEQ ID NO: 64, were synthesized and ligated into the antibody expression vector BPJPuro.

[0158] The resulting expression vector encoding the heavy and light chains was transfected into the CHO line (CHO SA, Cellectis SA, Paris, France) using liposome mediated transfection. Stable transfectants were isolated by puromycin selection and subcloned to provide clonal cell lines. Candidate cell lines were adapted to serum free suspension culture and screened for IgG production and robust growth. One of the cell lines was selected and named AT-1501, the cell line was cultured in a pilot scale bioreactor and the antibody AT-1501 was purified from conditioned medium by sequential concentration, Protein A/G affinity chromatography, and size exclusion chromatography.

[0159] A three-part sandwich ELISA assay was used to determine bindingkinetics of the AT-1501 antibody relative to the parental antibody hu5c8. All washes were performed using 3 washes of 250 µl of PBS. A 96-well polystyrene plate was coated with 100 µl/well of AT-1501 or hu5c8 antibody (2 µg/ml) for 16 hours at 4°C. The plate was washed and then blocked with 2% bovine serum albumin/PBS for 1 hour at room temperature. The plate was washed and recombinant human CD40L protein (Santa Cruz Biotechnology, Santa Cruz, California, USA) was added to the plate titrated out by 2-fold dilution starting at 2000 ng/ml. After binding and washing, the bound CD40L protein was detected using 100 µl a biotinylated goat anti-human CD40L polyclonal antibody (200 ng/ml) and 100 µl a streptavidin-horseradish peroxidase conjugate at 100 ng/ml. Colorimetric detection was performed with the chromagen TMB (3,3′,5,5′-tetramethylbenzidine) and spectrophotometric analysis of

absorption at 450 nm. The resulting binding curves (FIG. 6) show that AT-1501 (circle) has highly similar CD40L binding relative to the parental antibody hu5c8 (square). The control protein CTLA4-IgG1 (triangle), having the same Fc domain as AT-1501 showed no significant binding. The calculated EC50 for hu5c8 and AT-1501 is 114 and 137 nM, respectively. AT-1501-R28K and AT-1501-K74R showed binding similar to that of AT-1501.

[0160] In order to make a comparison of CD40L binding of antibodies from all 16 clones versus 5c8 or AT-1501 (also known as tegoprubart, a humanized monoclonal antibody that inhibits CD40 ligand) a binding assay was run using 2 clones with 5c8 and AT-1501 run on the same 96-well assay plate. A three-part sandwich ELISA assay was used to determine the level of binding of the antibodies of the present disclosure in comparison to reference antibodies 5c8-19 and AT-1501. 96-well polystyrene plates were coated with recombinant human CD40L (BioLegend Cat. # 591706) using 2 μg/ml in PBS and 50 μl/well was added to Costar 96-well ½ area high binding assay plates (Corning 3690) and incubated overnight at 4°C. Plates were blocked with (1X) PBS/1.0%BSA (140 μl/well) for 1 hour at room temperature to prevent background binding. Binding curves of 5C8 or AT1501 (from 2 μg/ml out serial 2-fold dilutions) were added (50 μl/well) and incubated for 1 hour at room temperature. Plates were washed and incubated with HRP-(Fab2) donkey anti-human IgG (Fc specific) (Jackson Immuno. 709-036-098) at a 1:10,000 dilution (50 μl/well) for 1 hour at room temperature. Plates were washed and TMB substrate (Surmodics BioFX TMBW-1000-01) was added (50 μl/well). Color development was stopped after 5 minutes at room temperature with 25 μl $2NH_2SO_4$. Plates were read on Molecular Devices SpectraMax M5 plate reader using SoftMax Pro 6.2.2 program to determine absorbance at 450 nm.

[0161] Relative CD40L binding potency was calculated as follows: [IC50 (clone)/ IC50 (5c8 or AT-1501) X 100%]. The ranked potency of the 16 clones versus 5c8 is shown in FIG. 7A and the ranked potency versus AT-1501 is shown in FIG. 7B. The resulting binding curves are shown in FIGs. 8A-8Q (comparison of 16 clones versus 5c8, FIG. 8H shows the comparison between AT-1501 and 5c8) and FIGs. 9A-9Q (comparison of the 16 clones versus AT-1501, FIG. 9H shows the comparison between AT-1501 and 5c8). The IC50, LCL, UCL and Relative Potency for each clone are shown in Table 1 (comparison with 5c8) and Table 2 (comparison with AT-1501).

Table 1.

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
8A	16-3	0.022	0.017	0.026	46
	5c8	0.047	0.040	0.054	
8B	8-3	0.036	0.028	0.043	51
	5c8	0.070	0.062	0.078	
8C	12-4	0.020	0.013	0.027	47
	5c8	0.042	0.038	0.046	
8D	8-4	0.036	0.030	0.041	51
	5c8	0.070	0.062	0.078	
8E	13-2	0.020	0.013	0.027	48
	5c8	0.041	0.038	0.045	
8F	4-4	0.037	0.029	0.045	51
	5c8	0.072	0.064	0.081	
8G	17-1	0.028	0.023	0.033	63
	5c8	0.044	0.036	0.053	
8H	AT-1501	0.049	0.043	0.056	95
	5c8	0.052	0.046	0.058	
8I	5-3	0.055	0.047	0.063	76
	5c8	0.072	0.064	0.081	
8J	6-6	0.065	0.059	0.070	106
	5c8	0.061	0.054	0.068	
8K	18-2	0.041	0.036	0.046	92
	5c8	0.044	0.036	0.053	
8L	10-4	0.075	0.065	0.086	113
	5c8	0.067	0.058	0.076	
8M	10-1	0.079	0.070	0.089	119
	5c8	0.067	0.058	0.076	
8N	7-5	0.102	0.094	0.111	168
	5c8	0.061	0.054	0.068	
8O	15.4	0.063	0.056	0.069	133
	5c8	0.047	0.040	0.054	
8P	11-5	0.092	0.071	0.112	177
	5c8	0.052	0.046	0.058	

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
8Q	15-1	0.081	0.073	0.089	163
	5c8	0.050	0.046	0.053	

Table 2.

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
9A	12-4	0.020	0.013	0.027	45
	AT-1501	0.044	0.039	0.049	
9B	8-3	0.036	0.028	0.043	59
	AT-1501	0.060	0.053	0.068	
9C	13-2	0.020	0.013	0.027	45
	AT-1501	0.044	0.038	0.049	
9D	8-4	0.036	0.030	0.041	59
	AT-1501	0.060	0.053	0.068	
9E	16-3	0.022	0.017	0.026	48
	AT-1501	0.045	0.039	0.051	
9F	4-4	0.037	0.029	0.045	60
	AT-1501	0.062	0.054	0.070	
9G	17-1	0.028	0.023	0.033	66
	AT-1501	0.042	0.035	0.050	
9H	5c8	0.052	0.046	0.058	105
	AT-1501	0.049	0.043	0.056	
9I	5-3	0.055	0.047	0.063	89
	AT-1501	0.062	0.054	0.070	
9J	10-4	0.075	0.065	0.086	115
	AT-1501	0.066	0.056	0.076	
9K	18-2	0.041	0.036	0.046	96
	AT-1501	0.042	0.035	0.050	
9L	10-1	0.079	0.070	0.089	121
	AT-1501	0.066	0.056	0.076	
9M	6-6	0.065	0.059	0.070	132
	AT-1501	0.049	0.047	0.051	
9N	11-5	0.092	0.071	0.112	174
	AT-1501	0.053	0.050	0.056	

Fig. No.	Clone	IC50	LCL	UCL	Rel. Pot.
9O	15-4	0.063	0.056	0.069	139
	AT-1501	0.045	0.039	0.051	
9P	7-5	0.102	0.094	0.111	210
	AT-1501	0.049	0.047	0.051	
9Q	15-1	0.081	0.073	0.089	159
	AT-1501	0.051	0.046	0.055	

[0162] The 16 VH/VL antibody clones constructed with an IgG1 Fc having two mutations P238S and N297G (SEQ ID NO: 75). These antibody clones were assayed for Fc effector function for binding to human FcγRI, FcγRIIa and FcγRIIIa.

[0163] Anti-CD40L antibodies (Abatacept included as negative control) were diluted to 2 μg/ml in (1X) PBS and 50 μl/well was added to Costar 96-well ½ area high binding assay plates (Corning 3690) for overnight incubation at 4°C. Plates were blocked with (1X) PBS/1.0% BSA (140 μl/well) for 1 hour at room temperature to prevent background binding. Binding curves of recombinant human FcγRI, IIa, IIIa and IIIb (from 5 μg/ml out serial 2-fold dilutions) were added (50 μl/well) and incubated for 1 hour at room temperature. Plates were washed and incubated with mouse anti-human CD16 (anti-FcRIII); CD32 (anti-FcRIIa) or CD64 (anti-FcRI) (eBioSciences/Invitrogen 14-0168-82; 16-0329-81; 14-0649-82) at 2 μg/ml (50 μl/well) for 1 hour at room temperature. Plates were washed and incubated with HRP- (Fab_2) goat anti-mouse IgG (Fc specific) (Jackson Immuno. 116-036-071) at a 1:10,000 dilution (50 μl/well) for 1 hour at room temperature. Plates were washed and TMB substrate (Surmodics BioFX TMBW-1000-01) was added (50 μl/well). Color development was stopped after 5 minutes at room temperature with (25 μl/well) $2NH_2SO_4$. Plates were read on Molecular Devices SpectraMax M5 plate reader using SoftMax Pro 6.2.2 program to determine absorbance at 450 nm.

[0164] As can be seen in the figures, the clones disclosed in this application were negative for binding to the three Fc receptors while 5c8 bound to FcγRI, FcγRIIa but not to FcγRIIIa or FcγRIIIb. Each of FIGs. 10A and 10B show the binding to FcγRIa for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. Each of FIGs. 11A and 11B show the binding to FcγRIIa for eight antibody clones compared with the binding curve of 5c8, AT-1501 and Abatacept. Each of FIGs.

12A and 12B show the binding to FcγRIIIa for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. Each of FIGs. 12C and 12D show the binding to FcγRIIIb for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. (FIGs. 10A, 11A, 12A and 12B show results from antibody clones 4-4, 5-3, 6-6, 7-5, 8-3, 8-4, 10-1 and 10-4; FIGs. 10B, 11B, 12C, and 12D show results from antibody clones 11-5, 12-4, 13-2, 15-1, 15-4, 16-3, 17-1 and 18-2).

[0165] Anti-CD40L antibodies (Abatacept included as negative control) were diluted to 2 μg/ml in (1X) PBS and 50 μl/well was added to Costar 96-well ½ area high binding assay plates (Corning 3690) for overnight incubation at 4°C. Plates were blocked with (1X) PBS/1.0% BSA (140 μl/well) for 1 hour at room temperature to prevent background binding. Binding curves of natural human C1q protein (Abcam ab96363) from 10 μg/ml out serial 2- fold dilutions were added (50 μl/well) for 1 hour at room temperature. Plates were washed and HRP-sheep anti-human C1q (Abcam ab46191) was added at a 1:400 dilution (50 μl/well) and incubated for 1 hour at room temperature. Plates were washed and TMB substrate (Surmodics BioFX TMBW-1000-01) is added (50 μl/well). Color development was stopped after 5 minutes at room temperature with (25 μl/well) $2NH_2SO_4$. Plates were read on Molecular Devices SpectraMax M5 plate reader using SoftMax Pro 6.2.2 program to determine absorbance at 450 nm.

[0166] As can be seen in the figures, the antibody from all sixteen antibody clones disclosed in this application were negative for binding to C1q while 5c8 showed significant binding. Each of FIGs. 13A and 13B show the binding to C1q for eight antibody clones compared with the binding curves of 5c8, AT-1501 and Abatacept. FIG. 13A shows results from antibody clones 4-4, 5-3, 6-6, 7-5, 8-3, 8-4, 10-1 and 10-4; FIG. 13B shows results from antibody clones 11-5, 12-4, 13-2, 15-1, 15-4, 16-3, 17-1 and 18-2.

[0167] Because the genetic expression data indicated the involvement of the co-stimulatory pathway, the efficacy of MRI was evaluated in the G93A model. MR1 binds to CD40L thus blocking its interaction of CD40 which participates in the co-stimulatory pathway involved in an immune response. It has been reported in the literature that MR1 is efficacious for the treatment of rheumatoid arthritis and graft versus host disease both of which have a strong immunologic component. Rheumatoid

arthritis is an autoimmune disease and graft versus host disease arises when the host's body mounts a vigorous immune response against the graft tissue.

Methods of Treatment

[0168] The present disclosure provides methods of treating a patient with an autoimmune disorder, including a kidney related autoimmune disorder, such as a kidney-related disease, disorder, or complication by administering to the patient a compound that blocks the interaction of CD40L and CD40 and/or blocks the interaction of CD28 and CD80 and/or blocks the interaction of CD28 and CD86. In some embodiments, the methods include treating a patient having colitis, drug induced lupus nephritis, lupus nephritis, nephropathy, chronic kidney disease, graft versus host disease, renal transplantation, immune graft response, transplant rejection, atherosclerosis, diabetic kidney disease, acute kidney injury, kidney failure, polycystic kidney disease, hematuria, Fabry disease, lupus kidney disease, Alport's syndrome, IgM nephropathy, interstitial nephritis, Membranoproliferative Glomerulonephritis, simple kidney cysts, kidney infections, kidney stones, or IgA nephropathy, by administering to the patient a compound that blocks the interaction of CD40L and CD40. In some embodiments, the methods include treating a patient by administering an anti-CD40L antibody. In some embodiments, the methods include treating a patient having an autoimmune disease. Non-limiting examples of autoimmune diseases include systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, and Graves' disease.

[0169] The present disclosure provides methods of treating a patient with an autoimmune disorder, including a kidney related autoimmune disorder, such as a kidney-related disease, disorder, or complication by administering to the patient an antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand . In some embodiments, the antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand and b) an Fc domain as described herein (see Table 4). In some embodiments, the antibody or antigen binding

fragment thereof comprises a) means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked and b) an Fc domain as described herein (see Table 4).

[0170] The present disclosure also provides methods of restoring kidney function to normal levels. Thus, for example, a kidney transplant is restored to normal kidney function levels. Kidney function may be determined using an estimated glomerular filtration rate (eGFR), where an eGFR level of greater than 90 is a normal level, e.g., for subjects under 60 their average eGFR is greater than 90. Distributions of eGFRs using standard of care tacrolimus following kidney transplant are typically around 51 mL/min/1.73 m^2 after the first year (FIG. 19). eGFR levels from 0-15 are indicative of kidney failure, from 15-60 are indicative of kidney disease, from 60-90 are indicative of early stage kidney disease, and above 90 is normal levels. These values can vary based on age (see Table 3). In adults, normal eGFR values are typically greater than 90, but this declines with age (see Table 3). For example, in some embodiments, levels of eGFR may be considered normal as shown in Table 3.

Table 3.

Age (years)	Average eGFR	eGFR Range
20-29	116	112-121
30-39	107	103-111
40-49	99	95-102
50-59	93	89-96
60-69	85	80-88
70+	75	71-79

[0171] In aspects of the methods described herein, the methods restore kidney function as measured by eGFR to levels greater than 50 mL/min/1.73 m^2, such as 50, 55, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 mL/min/1.73 m^2, or greater, or an amount within a range defined by any two of the aforementioned values. In some embodiments, the methods described herein restore kidney function to normal levels following kidney transplant or following kidney damage, such as levels greater than 90 mL/min/1.73 m^2, or similar

adjustments of eGFR values based on age. In some embodiments, the methods include restoring kidney function to a level that would be considered normal following kidney transplant or kidney damage, as measured by eGFR. As used herein, the term "restore" has its ordinary meaning as understood by those of skill in the art, and refers to achieving a level of eGFR that is not statistically significantly different from a reference level, such as a normal level. As used herein, a normal level of kidney function refers to a level considered by those of skill in the art to be a typically functioning kidney in a healthy individual, as measured by eGFR. In some embodiments, a normal level is a level of kidney function as measured by eGFR is set forth in Table 3, including a level within at least 5%, at least 10%, at least 15%, or at least 20% of the average reported values in Table 3. In some embodiments, a normal level is a level of kidney function as measured by the exemplary eGFR ranges as set forth in Table 3.

[0172] The present disclosure also provides methods of restoring kidney function in a subject having a kidney transplant, wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of an antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand. In some embodiments, the antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand and b) an Fc domain as described herein (see Table 4). In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked and b) an Fc domain as described herein (see Table 4).

[0173] Therapeutic compounds provided herein include any compound that blocks the interaction of CD40 with CD40L. For example, a number of animal studies describe agents capable of interrupting CD40:CD40L binding (see for example US2005158314 and US7173046 which are hereby incorporated by reference). Numerous anti-CD40L antibodies have been produced and characterized (see, e.g., U.S. Pat. No. 5,876,950) to Bristol-Myers Squibb, which is hereby incorporated by reference). Anti-CD40L antibodies useful in the methods of the present disclosure include, but are not limited to, MR1, a hamster monoclonal antibody available from Taconic (Hudson, NY) and BD Biosciences (San Jose, CA); 5c8, a humanized antibody described in U.S. Pat. No.

5,474,771 (which is hereby incorporated by reference); a hamster human chimeric antibody, IDEC 131/E6040 is a humanized monoclonal antibody comprising human gamma-1 heavy chains and human kappa-light chains with CDRs of murine monoclonal antibody clone 24-31, commercially available from Ancell (catalog X 353-020, Bayport, Minn.); ABI 793;, Sgn-40; ImxM90 (Immunex); ImxM91 (Immunex); ImxM92 (Immunex); and an anti-CD40L mAb commercially available from Genzyme (Cambridge, Mass., catalog No. 80-3703-01). Also commercially available is an anti-CD40L mAb from PharMingen (San Diego, Catalog #33580D). Embodiments according to the disclosure include methods of treating a patient with a kidney-related autoimmune disease, disorder, or complication, comprising administering a therapeutically effective amount of any compound capable of binding to CD40L, such as an anti-CD40L antibody. In some embodiments, the methods include treating a patient with a kidney-related autoimmune disease, disorder, or complication, comprising administering a therapeutically effective amount of an anti-CD40L antibody selected from MR1, 5c8, IDEC 131/E6040, clone 24-31, ABI 793, ImxM90, ImxM91, ImxM92, or Sgn-40. In some embodiments, the antibody is 5c8. In some embodiments, the antibody is MR1.

[0174] Additional examples of therapeutic compounds provided herein include an antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand. In some embodiments, the antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand and b) an Fc domain as described herein (see Table 4). In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked and b) an Fc domain as described herein (see Table 4).In some embodiments the disease, disorder, or complication is colitis, drug induced lupus nephritis, lupus nephritis, nephropathy, chronic kidney disease, graft versus host disease, renal transplantation, immune graft response, transplant rejection, atherosclerosis, diabetic kidney disease, acute kidney injury, kidney failure, polycystic kidney disease, hematuria, Fabry disease, lupus kidney disease, Alport's syndrome, IgM nephropathy, interstitial nephritis, Membranoproliferative

Glomerulonephritis, simple kidney cysts, kidney infections, kidney stones, or IgA nephropathy, by administering to the patient a compound that blocks the interaction of CD40L and CD40. In some embodiments, the methods of treating a patient include administering an anti-CD40L antibody. In some embodiments, the methods include treating a patient having an autoimmune disease. Non-limiting examples of autoimmune diseases include systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, and Graves' disease. In some embodiments, the anti-CD40L antibody is MR1. In some embodiments, the anti-CD40L antibody is 5c8.

[0175] In some embodiments, the methods include administering a therapeutically effective amount of an anti-CD40 antibody. In some embodiments the anti- CD40L compounds are Fab fragments, $F(ab')_2$, F(ab'), single chain antibodies, polypeptides, fusion constructs of polypeptides and the like. In some embodiments, the compounds are small molecule compounds that are capable of blocking the CD40:CD40L interaction. In some embodiments, these compounds include BIO3417, or any of the compounds disclosed in United States Patent Number 7,173,046, having the ability to block the CD40:CD40L interaction.

[0176] The compounds that block the CD40:CD40L interaction may be administered in combination with other compounds. Thus, in some embodiments, the methods of treating a patient as described herein include administering a compound that blocks the interaction of CD40L and CD40 in combination with a compound that blocks the interaction between CD80 and CD28. In some embodiments, the methods include administering a compound that blocks the interaction of CD40L and CD40 in combination with a compound that blocks the interaction between CD86 and CD28. In some embodiments, the compound that blocks the interaction of CD80 and CD28 is galiximab, or H1f1 & h3d1, or 16C10, or 7C10. In some embodiments, the compound that blocks the interaction between CD86 and CD28 is a CTLA4-Ig protein conjugate, such as abatacept or belatacept. Embodiments according to the present disclosure also include methods of treating a patient with an autoimmune disorder, such as a kidney associated autoimmune disorder, including kidney- related disease, disorder, or complication comprising administering a compound that blocks the interaction of

CD40L and CD40 in combination with a compound that blocks the interaction between CD80 and CD28 or administering a therapeutically effective amount of a compound that blocks the interaction of CD40L and CD40 in combination with a compound that blocks the interaction between CD86 and CD28, wherein the kidney-related disease, disorder or complication is colitis, drug induced lupus nephritis, lupus nephritis, nephropathy, chronic kidney disease, graft versus host disease, renal transplantation, immune graft response, transplant rejection, atherosclerosis, diabetic kidney disease, acute kidney injury, kidney failure, polycystic kidney disease, hematuria, Fabry disease, lupus kidney disease, Alport's syndrome, IgM nephropathy, interstitial nephritis, Membranoproliferative Glomerulonephritis, simple kidney cysts, kidney infections, kidney stones, or IgA nephropathy, by administering to the patient a compound that blocks the interaction of CD40L and CD40. In some embodiments, the methods include administering an anti-CD40L antibody. In some embodiments, the methods include treating a patient having an autoimmune disease. Non-limiting examples of autoimmune diseases include systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, and Graves' disease. In some embodiments, the compound that blocks the interaction of CD40L and CD40 is MR1 and the compound that blocks the interaction between CD28 and CD86 or between CD28 and CD80 is abatacept, galiximab or belatacept. In some embodiments, the compound that blocks the interaction of CD40L and CD40 is 5c8. In some embodiments, the methods include administering a therapeutically effective amount of MR1 in combination with abatacept or belatacept. In some embodiments, the methods include administering a therapeutically effective amount of 5c8 in combination with abatacept or belatacept.

Autoimmune diseases, disorders, and conditions

[0177] The methods described herein relate to treatments of subjects with one or more autoimmune disease, or a tissue transplant. In some embodiments, the disease or disorder includes a kidney-related autoimmune disease, disorder, and/or condition. In some embodiments, the autoimmune disease is a kidney-related disease, disorder, or condition. In some embodiments, the kidney-related disease, disorder, or condition is a complication following a kidney transplant. In some embodiments, the kidney-related

disease, disorder, or condition is kidney transplant rejection. In some embodiments, the kidney-related disease, disorder, or condition is graft-vs-host disease. In some embodiments, the kidney-related disease, disorder, or condition is a chronic kidney disease. In some embodiments, the kidney-related disease, disorder, or condition is a nephropathy. In some embodiments, the kidney-related disease, disorder, or condition is IgA nephropathy. In some embodiments, the kidney-related disease, disorder, or condition is an autoimmune disease of the kidney. In some embodiments, the kidney-related disease, disorder, or condition is inflammation or involves inflammation. In some embodiments, the transplant is a tissue transplant, such as kidney transplant.

[0178] It will be understood that the compounds disclosed herein targeting CD40 or CD40L can be used against any disease, disorder, or condition in which the kidney is impaired. Non-limiting examples of kidney-related diseases, disorders, and conditions include: colitis, drug induced lupus nephritis, lupus nephritis, nephropathy, chronic kidney disease, graft versus host disease, renal transplantation, immune graft response, transplant rejection, atherosclerosis, diabetic kidney disease, acute kidney injury, kidney failure, polycystic kidney disease, hematuria, Fabry disease, lupus kidney disease, Alport's syndrome, IgM nephropathy, interstitial nephritis, Membranoproliferative Glomerulonephritis, simple kidney cysts, kidney infections, kidney stones, IgA nephropathy, systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, Graves' disease, Abderhalden–Kaufmann–Lignac syndrome (Nephropathic Cystinosis), Abdominal Compartment Syndrome, Acetaminophen-induced Nephrotoxicity, Acute Kidney Failure/Acute Kidney Injury, Acute Injury with Loin Pain after Anaerobic Exercise (ALPE), Renal Hypouricemia, Acute Lobar Nephronia, Acute Phosphate Nephropathy, Acute Tubular Necrosis, Adenine Phosphoribosyltransferase Deficiency, Adenovirus Nephritis, Alagille Syndrome, Alkaptonuria, Alport Syndrome, Alstrom Syndrome, Amyloidosis, ANCA Vasculitis Related to Endocarditis and Other Infections, Angiomyolipoma, Anabolic Steroid Abuse, Analgesic Nephropathy, Anorexia Nervosa and Kidney Disease, Angiotensin Antibodies and Focal Segmental Glomerulosclerosis, Anticoagulant-related Nephropathy, Antiphospholipid Syndrome, Anti-LRP2 Nephropathy, Anti-Brush Border Nephropathy, Anti-TNF-α Therapy-related Glomerulonephritis, APOL1

Mutations, Apparent Mineralocorticoid Excess Syndrome, Aristolochic Acid Nephropathy, Chinese Herbal Nephropathy, Balkan Endemic Nephropathy, Arteriovenous Malformations and Fistulas of the Urologic Tract, Atypical Hemolytic Uremic Syndrome, Autosomal Dominant Hypocalcemia, Bardet-Biedl Syndrome, Bartter Syndrome, Bath Salts and Acute Kidney Injury, Beer Potomania, Beeturia, β-Thalassemia Renal Disease, Bile Cast Nephropathy, Birt-Hogg-Dubé Syndrome, BK Polyoma Virus Nephropathy in the Native Kidney, Bladder Rupture, Bladder Sphincter Dyssynergia, Bladder Tamponade, Bodybuilder's Glomerulopathy, Border-Crossers' Nephropathy, Bourbon Virus and Acute Kidney Injury, BRASH Syndrome, Acute Renal Dysfunction, Byetta and Renal Failure, C1q Nephropathy, C3 Glomerulopathy, C4 Glomerulopathy, CAKUT (Congenital Anomalies of the Kidney and Urologic Tract), Calyceal Diverticulum, Calcineurin Inhibitor Nephrotoxicity, Callilepsis Laureola Poisoning, Cannabinoid Hyperemesis Acute Renal Failure, Capillary Leak Syndrome, Carconoid Syndrome and Renal Failure, Cardiorenal syndrome, Carfilzomib- Induced Renal Injury, CFHR5 nephropathy, Charcot–Marie–Tooth Disease with Glomerulopathy, Cholesterol Emboli, Churg–Strauss syndrome, Chyluria, Ciliopathy, Cisplatin Nephrotoxicity, Cold Diuresis, Colistin Nephrotoxicity, Collagenofibrotic Glomerulopathy, Collapsing Glomerulopathy, Collapsing Glomerulopathy Related to CMV, Combination Antiretroviral (cART) Related-Nephropathy, Congenital Adrenal Hyperplasia, 17-Alpha-Hydroxylase/7 20-Lyase Deficiency, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT), Congenital Nephrotic Syndrome, Congestive Renal Failure, Conorenal syndrome (Mainzer-Saldino Syndrome or Saldino-Mainzer Disease), Contrast Nephropathy, Copper Sulphate Intoxication, Coronavirus (COVID-19) Associated Kidney Failure and Kidney Disease, Cortical Necrosis, Crizotinib-related Acute Kidney Injury, Crying Kidneys, Cryocrystalglobulinemia, Cryoglobuinemia, Crystalglobulin-Induced Nephropathy, Crystal-Storing Histiocytosis, Cystic Kidney Disease, Acquired, Cystic Kidney Disease, Localized, Renal Failure, Cystinuria, Cystinosis, Dasatinib-Induced Nephrotic-Range Proteinuria, Deferasirox (Exjade) Nephrotoxicity, Dense Deposit Disease (MPGN Type 2), Dent Disease (X-linked Recessive Nephrolithiasis), DHA Crystalline Nephropathy, Dialysis Disequilibrium Syndrome, Diabetic Kidney Disease, Diffuse Mesangial Sclerosis, Diuresis, Djenkol Bean Poisoning (Djenkolism), Duplicated Ureter, EAST syndrome, Ectopic Kidney, Edema, Swelling, End-Stage

Kidney Disease, Erdheim-Chester Disease, Fabry's Disease, Familial Hypocalciuric Hypercalcemia, Fanconi Syndrome, Fraser syndrome, Fibronectin Glomerulopathy, Fibrillary Glomerulonephritis and Immunotactoid Glomerulopathy, Fibrillary Glomerulonephritis, Congophilic, Fraley syndrome, Fluid Overload, Hypervolemia, Focal Segmental Glomerulosclerosis, Focal Sclerosis, Focal Glomerulosclerosis, Focal Segmental Glomerulosclerosis (Familial) with Complete Heart Block, Galloway Mowat syndrome, Giant Cell (Temporal) Arteritis with Kidney Involvement, Gestational Hypertension, Gitelman Syndrome, Glomerular Diseases, Glomerular Tubular Reflux, Glomerulonephritis, Glycosuria, Goodpasture Syndrome, Green Smoothie Cleanse Nephropathy, HANAC Syndrome, Harvoni (Ledipasvir with Sofosbuvir)-Induced Renal Injury, Hair Dye Ingestion and Acute Kidney Injury, Hantavirus Infection Podocytopathy, Heat Stress Nephropathy, Hematuria (Blood in Urine), Hemolytic Uremic Syndrome (HUS), Atypical Hemolytic Uremic Syndrome (aHUS), Hemophagocytic Syndrome, Hemorrhagic Cystitis, Hemorrhagic Fever with Renal Syndrome (HFRS, Hantavirus Renal Disease, Korean Hemorrhagic Fever, Epidemic Hemorrhagic Fever, Nephropathis Epidemica), Hemosiderinuria, Hemosiderosis related to Paroxysmal Nocturnal Hemoglobinuria and Hemolytic Anemia, Hepatic Glomerulopathy, Hepatic Veno-Occlusive Disease, Sinusoidal Obstruction Syndrome, Hepatitis C-Associated Renal Disease, Hepatocyte Nuclear Factor 1β– Associated Kidney Disease, Hepatorenal Syndrome, Herbal Supplements and Kidney Disease, High Altitude Renal Syndrome, High Blood Pressure and Kidney Disease, HIV-Associated Immune Complex Kidney Disease (HIVICK), HIV-Associated Nephropathy (HIVAN), Holocaust Kidney Disease, HNF1B-related Autosomal Dominant Tubulointerstitial Kidney Disease, Horseshoe Kidney (Renal Fusion), Hunner's Ulcer, Hydrophilic Polymer Emboli, Hydroxychloroquine-induced Renal Phospholipidosis, Hyperaldosteronism, Hypercalcemia, Hyperkalemia, Hypermagnesemia, Hypernatremia, Hyperoxaluria, Hyperphosphatemia, Hypocalcemia, Hypocomplementemic Urticarial Vasculitic Syndrome, Hypokalemia, Hypokalemia-induced renal dysfunction, Hypokalemic Periodic Paralysis, Hypomagnesemia, Hyponatremia, Hypophosphatemia, Hypertension, Hypertension, Monogenic, Iced Tea Nephropathy, Ifosfamide Nephrotoxicity, IgA Nephropathy, IgG4 Nephropathy, Immersion Diuresis, Immune-Checkpoint Therapy-Related Interstitial Nephritis, Infliximab-Related Renal Disease, Interstitial Cystitis, Painful

Bladder Syndrome, Interstitial Nephritis, Interstitial Nephritis, Karyomegalic, Ivemark's syndrome, JC Virus Nephropathy, Joubert Syndrome, Ketamine-Associated Bladder Dysfunction, Kidney-Based Immune Disorders, Kidney Stones, Nephrolithiasis, Kidney Stones due to Light Chains, Kimura Disease, Kombucha Tea Toxicity, Lead Nephropathy and Lead-Related Nephrotoxicity, Lecithin Cholesterol Acyltransferase Deficiency (LCAT Deficiency), Leptospirosis Renal Disease, Light Chain Deposition Disease, Monoclonal Immunoglobulin Deposition Disease, Light Chain Proximal Tubulopathy, Liddle Syndrome, Lightwood- Albright Syndrome, Lipoprotein Glomerulopathy, Lithium Nephrotoxicity, LMX1B Mutations Cause Hereditary FSGS, Loin Pain Hematuria, Lupus, Systemic Lupus Erythematosis, Lupus Kidney Disease, Lupus Nephritis, Lupus Nephritis with Antineutrophil Cytoplasmic Antibody Seropositivity, Lupus Podocytopathy, Lupus-like Nephritis, Lupus Nephritis, Lyme Disease-Associated Glomerulonephritis, Lysinuric Protein Intolerance, Lysozyme Nephropathy, Malarial Nephropathy, Malignancy-Associated Renal Disease, Malignant Hypertension, Malakoplakia, Marfan Syndrome and Kidney Disease, McKittrick- Wheelock Syndrome, Meatal Stenosis, Medullary Cystic Kidney Disease, Urolodulin- Associated Nephropathy, Juvenile Hyperuricemic Nephropathy Type 1, Medullary Sponge Kidney, Megaureter, MELAS Syndrome, Membranoproliferative Glomerulonephritis, Membranous Nephropathy, Membranous Nephropathy with Spherules, Membranous-like Glomerulopathy with Masked IgG Kappa Deposits, MesoAmerican Nephropathy, Metabolic Acidosis, Metabolic Alkalosis, Methotrexate-related Renal Failure, Microscopic Polyangiitis, Milk-alkalai syndrome, Minimal Change Disease, Monoclonal Gammopathy of Renal Significance, Dysproteinemia, Mouthwash Toxicity, MUC1 Nephropathy, Multicystic dysplastic kidney, Multiple Myeloma, Myeloproliferative Neoplasms and Glomerulopathy, Nail-patella Syndrome, NARP Syndrome, Nephrocalcinosis, Nephrocystin-1 Gene Deletions and ESRD, Nephrogenic Systemic Fibrosis, Nephronophthisis due to Nephrocystin-1 Gene Deletions, Nephroptosis (Floating Kidney, Renal Ptosis), Nephrotic Syndrome, Neurogenic Bladder, Nodular Glomerulosclerosis, Non-Gonococcal Urethritis, Nutcracker syndrome, Oligomeganephronia, Orofaciodigital Syndrome, Orotic Aciduria, Orthostatic Hypotension, Orthostatic Proteinuria, Osmotic Diuresis, Osmotic Nephrosis, Ovarian Hyperstimulation Syndrome, Oxalate Nephropathy, Page Kidney, Papillary Necrosis, Papillorenal Syndrome (Renal-

Coloboma Syndrome, Isolated Renal Hypoplasia), The Peritoneal-Renal Syndrome, POEMS Syndrome, Posterior Urethral Valve, Podocyte Infolding Glomerulopathy, Post- infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Post-infectious Glomerulonephritis, Atypical, Post-Infectious Glomerulonephritis (IgA-Dominant), Mimicking IgA Nephropathy, Polyarteritis Nodosa, Polycystic Kidney Disease, Posterior Urethral Valves, Post-Obstructive Diuresis, Preeclampsia, Propofol infusion syndrome, Proliferative Glomerulonephritis with Monoclonal IgG Deposits (Nasr Disease), Propolis (Honeybee Resin) Related Renal Failure, Proteinuria (Protein in Urine), Pseudohyperaldosteronism, Pseudohypobicarbonatemia, Pseudohypoparathyroidism, Pseudoporphyria, Psoriasis and Kidney Disease, Pulmonary-Renal Syndrome, Purple Urine Bag Syndrome, Pyelonephritis (Kidney Infection), Pyonephrosis, Radiation Nephropathy, Refeeding syndrome, Reflux Nephropathy, Rapidly Progressive Glomerulonephritis, REN Mutations Causing Autosomal Dominant Tubulointerstitial Kidney Disease, Renal Abscess, Peripnephric Abscess, Renal Agenesis, Renal Arcuate Vein Microthrombi-Associated Acute Kidney Injury, Renal Artery Aneurysm, Renal Artery Dissection, Spontaneous, Renal Artery Stenosis, Renal Cell Cancer, Renal Cyst, Renal Hypouricemia with Exercise-induced Acute Renal Failure, Renal Infarction, Renal Osteodystrophy, Renal Tubular Acidosis, Renin Mutations and Autosomal Dominant Tubulointerstitial Kidney Disease, Renin Secreting Tumors (Juxtaglomerular Cell Tumor), Reset Osmostat, Retrocaval Ureter, Retroperitoneal Fibrosis, Rhabdomyolysis, Rhabdomyolysis related to Bariatric Surgery, Rheumatoid Arthritis-Associated Renal Disease, Rubraca (rucaparib)-related Increase in Creatinine, Sarcoidosis Renal Disease, Saturday Night Acute Kidney Injury, Schistosomiasis and Glomerular Disease, Schimke immuno-osseous dysplasia, Scleroderma Renal Crisis, Serpentine Fibula-Polycystic Kidney Syndrome, Exner Syndrome, Sézary Syndrome, Sickle Cell Nephropathy, Sjögren's Syndrome and Renal Disease, Sri Lankan Farmers' Kidney Disease, Star Fruit Nephrotoxicity, renal transplantation, Kidney Disease Following Hematopoietic Cell Transplantation, Kidney Disease Related to Stem Cell Transplantation, TAFRO Syndrome, Tea and Toast Hyponatremia, Tenofovir-Induced Nephrotoxicity, Thin Basement Membrane Disease, Benign Familial Hematuria, Thrombotic Microangiopathy Associated with Monoclonal Gammopathy, Trench Nephritis, Autosomal Dominant Thrombotic Microangiopathy and CKD, Trigonitis, Tuberous Sclerosis, Tuberous sclerosis

complex (TSC) and autosomal dominant polycystic kidney disease (ADPKD) (TSC2/PKD1 contiguous gene syndrome), Tubular Dysgenesis, Immune Complex Tubulointerstitial Nephritis, Tumor Lysis Syndrome, Uremia, Uremic Optic Neuropathy, Ureteritis Cystica, Ureterocele, Urethral Caruncle, Urethral Stricture, Urinary Incontinence, Urinary Tract Infection, Urinary Tract Obstruction, Urogenital Fistula, Vasomotor Nephropathy, Vesicointestinal Fistula,Vesicoureteral Reflux, Von Hippel-Lindau Disease, Waldenstrom's Macroglobulinemic Glomerulonephritis, Wegener's Granulomatosis, Granulomatosis with Polyangiitis, Wunderlich syndrome, Zellweger Syndrome, and Cerebrohepatorenal Syndrome.

Pharmaceutical compositions and methods of administration

[0179] To treat any of the foregoing disorders, pharmaceutical compositions for use in accordance with the methods of the present disclosure may be formulated in a conventional manner using one or more physiologically acceptable carriers. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there are a wide variety of suitable formulations of the compounds useful in the methods of the present disclosure (see, e.g., Remington: The Science and Practice of Pharmacy, 20th ed., Gennaro et al. Eds., Lippincott Williams and Wilkins, 2000).

[0180] Formulations suitable for oral administration include, for example, solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano- particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

[0181] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and nonaqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. For example, such compositions comprising a pharmaceutically acceptable carrier can comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins;

polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (e.g., aluminum hydroxide); and preservatives.

[0182] According to the present disclosure the compounds as described herein, such as antibodies and antigen binding fragments thereof, can be administered by any suitable means, which can vary, for example, depending on the type of disorder being treated and on the nature of the compound itself. For example, the compounds may be administered orally, parenterally, or topically. For proteins such as antibodies, administration routes preferably include parenteral, e.g., intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous. For example, the parenteral dosing is given by injection, including intravenous, intramuscular, or subcutaneous injection. The amount to be administered will depend on a variety of factors such as the clinical symptoms, weight of the individual, and whether other drugs are administered. It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration is within the level of ordinary skill in the pharmaceutical and medical arts, and is described below.

[0183] In one exemplary pharmaceutical composition containing an anti-CD40L antibody or antigen-binding fragment thereof described herein, the composition is formulated as a sterile, preservative-free solution of the anti-CD40L antibody or antigen-binding fragment thereof for intravenous or subcutaneous administration. The formulation may be supplied as either a single-use, prefilled pen, as a single-use, for example containing about 1 mL prefilled glass syringe, or as a single-use institutional use vial. For example, the pharmaceutical composition containing the antibody or antigen-binding fragment thereof that specifically binds CD40 ligand is clear and colorless, with a pH of about 5.0 to about 6.9, preferably a pH of about 5.0 to about 6.5, and even more preferably a pH ranging from about 5.0 to about 6.0. In various embodiments, the formulations comprising the pharmaceutical compositions may contain from about 500 mg to about 1 mg, or from about 400 mg to about 10 mg, or from about 300 mg to about 30 mg or from about 200 mg to about 50 mg of the anti-CD40L antibody or antigen-binding fragment thereof per mL of solution when reconstituted and administered to the subject.

[0184] Selecting an administration regimen for a therapeutic depends on several factors, including the serum or tissue turnover rate of the entity, the level of symptoms, the immunogenicity of the entity, and the accessibility of the target cells in the

biological matrix, general health of the patient, the prior medical history of the patient, and the like. Preferably, an administration regimen maximizes the amount of therapeutic delivered to the patient consistent with an acceptable level of side effects. Accordingly, the amount of biologic delivered depends in part on the particular entity and the severity of the condition being treated. It should be appreciated that determination of proper dosage forms, dosage amounts, and routes of administration is within the level of ordinary skill in the pharmaceutical and medical arts.

Doses and Exposure Levels

[0185] To treat a patient as described herein, the methods as described herein comprise, among other things, administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand.

[0186] In some embodiments, the therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered by an intravenous injection or infusion. In some embodiments, the therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered as a bolus, and the rest of the antibody dose is administered by intravenous injection or infusion. A predetermined dose of the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered, for example, over a period of an hour or two hours to five hours.

[0187] In some embodiments, the therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered by a subcutaneous injection and/or infusion in the form of a bolus and the rest by infusion of the antibody formulation. In some embodiments, the therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered as a bolus, and the rest of the antibody dose may be administered by subcutaneous or intravenous injection. A predetermined dose of the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered, for example, over a period of an hour, or a period of two hours, or a period of three hours, or a period of four hours, or a period of five hours or longer.

[0188] In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is selected based

on the target transplant tissue, which as described herein is a kidney. Whereas a similar or greater therapeutically effective amount may be used for kidneys as for transplant of other complex tissues, such as a different organ or xeno-tissue, differences in, among other things, vasculature or platelet activation, can provide different dosing considerations and strategies than for kidneys.

[0189] In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 200 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 100 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 90 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 80 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment is about 1 mg/kg to about 70 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 60 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 50 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 40 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 30 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 20 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 10 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 5 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 5 mg/kg to about 10 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 10 mg/kg to about 15 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 15 mg/kg to about 20 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 20 mg/kg to about

25 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 25 mg/kg to about 30 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 30 mg/kg to about 35 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 35 mg/kg to about 40 mg/kg.

[0190] In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 12.5 mg/kg, 15 mg/kg, 17.5 mg/kg, 20 mg/kg, 22.5 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, or 40 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 10 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 20 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 50 mg/kg.

[0191] In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 200 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 100 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 90 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 80 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 70 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 60 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 50 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 40 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 30 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 20 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 10 mg/kg. In some embodiments, the

therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg to 5 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 5 mg/kg to 10 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 10 mg/kg to 15 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 15 mg/kg to 20 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 20 mg/kg to 25 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 25 mg/kg to 30 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 30 mg/kg to 35 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 35 mg/kg to 40 mg/kg.

[0192] In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 12.5 mg/kg, 15 mg/kg, 17.5 mg/kg, 20 mg/kg, 22.5 mg/kg, 25 mg/kg, 30 mg/kg, 35 mg/kg, or 40 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 10 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 20 mg/kg. In some embodiments, the therapeutically effective amount of the antibody or antigen binding fragment thereof is 50 mg/kg.

[0193] In some embodiments, the antibody or antigen binding fragment thereof is administered at least once every 3 weeks. In some embodiments, the antibody or antigen binding fragment thereof is administered as a maintenance dose at least once every 3 weeks. In some embodiments, the antibody or antigen binding fragment thereof is administered at least once every 4 weeks. In some embodiments, the antibody or antigen binding fragment thereof is administered as a maintenance dose at least once every 4 weeks. In some embodiments, the antibody or antigen binding fragment thereof is administered 7 days, 5 days, or 4 days before transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered 3 days, 2 days, or 1 day before transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered the same day of transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered or more of 1 day, 2 days, 3 days, 4

days, 5 days, 6 days, or 7 days after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, or 21 days after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered every 21 ± 2 days after transplant, beginning on any one or more of day 0, 1, 3, 7, 14, 21, or 28 after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered every 28 ± 2 days after transplant, beginning on any one or more of day 0, 1, 3, 7, 14, 21, or 28 after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered on days -2, 0, 1, 3, 7, 14, 21, and 28 and every 21 ± 2 days thereafter after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered on days -2, 0, 1, 3, 7, 14, 21, and 28 and every 28 ± 2 days thereafter after transplant.

[0194] In some embodiments, the antibody or antigen binding fragment thereof is administered on days -2, 0, 1, 3, 7, 14, 21, and 28 and every 21 ± 2 days thereafter after transplant and the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 20 mg/kg.

[0195] In some embodiments, the antibody or antigen binding fragment thereof is administered for about 6 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 9 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 12 months after transplant or for longer than 12 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 15 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 18 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 21 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 24 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 3 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 4 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 5 years after transplant. In some embodiments, the antibody or antigen

binding fragment thereof is administered for about 6 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 7 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 8 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 9 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 10 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for more than about 10 years after transplant.

[0196] In some embodiments, the antibody or antigen binding fragment thereof is administered for 6 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 9 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 12 months after transplant or for longer than 12 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 15 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 18 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 21 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 24 months after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 3 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 4 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 5 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 6 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 7 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 8 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for 9 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for about 10 years after transplant. In some embodiments, the antibody or antigen binding fragment thereof is administered for more than about 10 years after transplant.

[0197] In some embodiments, the antibody or antigen binding fragment thereof improves the kidney function as measured by an aggregate mean estimated glomerular filtration rate (eGFR), using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. See, e.g., Levey AS et al., "A New Equation to Estimate Glomerular Filtration Rate," Ann. Intern. Med. 150:604-12 (2009); Inker LA et al., "New Creatinine- and Cystatin C-Based Equations to Estimate GFR Without Race," N. Engl. J. Med. 385:1737-49 (2021).

[0198] In some embodiments, the eGFR is at least about 50 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 55 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 60 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 65 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 70 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 75 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 80 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 85 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 90 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof.

[0199] In some embodiments, the eGFR is at least about 50 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 55 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 60 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 65 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In

some embodiments, the eGFR is at least about 70 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 75 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 80 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 85 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least about 90 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In each instance of after 1 year discussed above, a duration of 2, 3, 4, 5, 6, 7, 8, 9, or 10 years is also described.

[0200] In some embodiments, the antibody or antigen binding fragment thereof improves the kidney function as measured by an aggregate mean estimated glomerular filtration rate (eGFR). In some embodiments, the eGFR is at least 50 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 55 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 60 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 65 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 70 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 75 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 80 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 85 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 90 mL/min/1.73 m^2 after 90 days following the administration of the antibody or antigen binding fragment thereof.

[0201] In some embodiments, the antibody or antigen binding fragment thereof improves the kidney function as measured by an aggregate mean estimated glomerular filtration rate (eGFR). In some embodiments, the eGFR is at least 50 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 55 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 60 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 65 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 70 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 75 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 80 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 85 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In some embodiments, the eGFR is at least 90 mL/min/1.73 m^2 after 1 year following the administration of the antibody or antigen binding fragment thereof. In each instance of after 1 year discussed above, a duration of 2, 3, 4, 5, 6, 7, 8, 9, or 10 years is also described.

[0202] In some embodiments, the patient-to-donor HLA match is 0. In some embodiments, the patient-to-donor HLA match is 1. In some embodiments, the patient-to-donor HLA match is 2. In some embodiments, the patient-to-donor HLA match is 3. In some embodiments, the patient-to-donor HLA match is 4. In some embodiments, the patient-to-donor HLA match is 5. In some embodiments, the patient-to-donor HLA match is 6. In some embodiments, the patient-to-donor HLA match is 7. In some embodiments, the patient-to-donor HLA match is 8. In some embodiments, the patient-to-donor HLA match is 9. In some embodiments, the patient-to-donor HLA match is 10. An example of HLA match parameters and scoring is described in Williams, R.C., et al., “The Risk of Transplant Failure With HLA Mismatch in First Adult Kidney

Allografts From Deceased Donors Transplantation," Transplantation 100:1094-1102 (2016).

[0203] In some embodiments, the patient-to-donor HLA match is 3-6. In some embodiments, the patient-to-donor HLA match is 4-6. In some embodiments, the patient-to-donor HLA match is 4-5. In some embodiments, the patient-to-donor HLA match is 5-6.

[0204] In some embodiments, the donor organ is from a donor less than 70 years of age. In some embodiments, the donor organ is from a donor less than 60 years of age. In some embodiments, the donor organ is from a donor less than 50 years of age. In some embodiments, the donor organ is from a donor less than 40 years of age. In some embodiments, the donor organ is from a donor less than 30 years of age. In some embodiments, the donor organ is from a donor less than 20 years of age.

[0205] In some embodiments, the donor organ is from a donor between 20-50 years of age. In some embodiments, the donor organ is from a donor between 20-40 years of age. In some embodiments, the donor organ is from a donor between 20-30 years of age. In some embodiments, the donor organ is from a donor between 30-50 years of age. In some embodiments, the donor organ is from a donor between 30-40 years of age. In some embodiments, the donor organ is from a donor between 40-50 years of age.

[0206] In some embodiments, the subject is less than 80 years of age. In some embodiments, the subject is less than 70 years of age. In some embodiments, the subject is less than 60 years of age. In some embodiments, the subject is less than 50 years of age. In some embodiments, the subject is less than 40 years of age. In some embodiments, the subject is less than 30 years of age. In some embodiments, the subject is less than 20 years of age.

[0207] In some embodiments, the subject is 80-89 years of age. In some embodiments, the subject is 70-79 years of age. In some embodiments, the subject is 60-69 years of age. In some embodiments, the subject is 50-59 years of age. In some embodiments, the subject is 40-49 years of age. In some embodiments, the subject is 30-39 years of age. In some embodiments, the subject is 20-29 years of age. In some embodiments, the subject is 10-19 years of age.

[0208] In some embodiments, the subject has a body mass index (BMI) of less than 35. In some embodiments, the subject has a body mass index (BMI) of less than 30. In

some embodiments, the subject has a body mass index (BMI) of less than 25. In some embodiments, the subject has a body mass index (BMI) of less than 20.

[0209] In some embodiments, the subject has a body mass index (BMI) of about 18.5-24.9. In some embodiments, the subject has a body mass index (BMI) of about 25.0–29.9. In some embodiments, the subject has a body mass index (BMI) of about 30.0–34.9. In some embodiments, the subject has a body mass index (BMI) of about 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, or 35.

Combination Therapies

[0210] The antibody or antigen binding fragment thereof that specifically binds CD40 ligand as described herein can be administered alone (monotherapy) or in combination with other compounds. For example, in one embodiment the combination therapy may include one or more additional pharmaceutically effective compounds. In some embodiments, the one or more additional pharmaceutically effective compounds includes anti-thymocyte globulin, mycophenolate mofetil or mycophenolate sodium, or prednisone or a prednisone equivalent. In another embodiment the combination therapy includes standard of care treatment that may, or may not, include additional therapeutic agents (that is, consists essentially of the antibody or antibody fragment thereof).

[0211] Adjunctive or combined administration (co-administration) includes simultaneous administration of any of the antibodies or antigen binding fragments thereof, described herein and one or more agents in the same or different dosage form, or separate administration of the polypeptide and one or more agents (e.g., sequential administration). Such concurrent or sequential administration preferably results in both the polypeptide and the one or more agents being simultaneously present in treated patients.

[0212] In some embodiments, the one or more additional pharmaceutically effective compounds targets T-cells. In some embodiments, the one or more additional pharmaceutically effective compounds targets T-cells by one or more of: clearing T-cells from circulation or modulating T-cell activation, homing, or cytotoxic activities. In some embodiments, the compound that targets T-cells is an anti-thymocyte globulin (ATG). In some embodiments, the compound that targets T-cells is an inhibitor of mammalian target of rapamycin (mTOR). In some embodiments, the compound that

targets T-cells is an OX40 antibody. In some aspects, the compound that targets T-cells is an anti-CD2 antibody.

[0213] In some embodiments, the one or more pharmaceutically effective compound is anti-thymocyte globulin. In some embodiments, the anti-thymocyte globulin is sourced from a species other than humans. In some embodiments, the anti-thymocyte globulin is sourced from rabbit. In some embodiments, the anti-thymocyte globulin is sourced from horse. In some embodiments, the anti-thymocyte globulin is sourced from goat. In some embodiments, the anti-thymocyte globulin is sourced from pig. In some embodiments, a total of 1 mg/kg to 50 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 3.0 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 3.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 4.0 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 4.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In some embodiments, a total of 5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In some embodiments, a total of 5.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In some embodiments, a total of 6 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In some embodiments, a total of 6.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In some embodiments, a total of 7 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In some embodiments, a total of 7.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.. In

some embodiments, a total of 8 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 8.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 9 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 9.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 10 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 10.5 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 15 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 20 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant. In some embodiments, a total of 25 mg/kg of anti-thymocyte globulin is administered by IV infusion in divided doses beginning the day of transplant and continuing 5-10 days post-transplant.

[0214] In some embodiments, the one or more pharmaceutically effective compound that targets T cells inhibits binding of IL-2 to IL-2 receptors. In some embodiments, the compound that inhibits binding of IL-2 to IL-2 receptors is basiliximab. In some embodiments, basiliximab is administered as a 1 mg to 50 mg IV dose within 2 hours prior to transplant. In some embodiments, basiliximab is administered 5 mg IV on day 0 within 2 hours prior to transplant and 5 mg IV on day 4 post-transplant. In some embodiments, basiliximab is administered 10 mg IV on day 0 within 2 hours prior to transplant and 10 mg IV on day 4 post-transplant. In some embodiments, basiliximab is administered 15 mg IV on day 0 within 2 hours prior to transplant and 15 mg IV on day 4 post-transplant. In some embodiments, basiliximab is administered 20 mg IV on day 0 within 2 hours prior to transplant and 20 mg IV on day 4 post-transplant. In some

embodiments, basiliximab is administered 25 mg IV on day 0 within 2 hours prior to transplant and 25 mg IV on day 4 post-transplant.

[0215] In some embodiments, the one or pharmaceutically effective compound that targets T-cells inhibits mTOR. In some embodiments, the compound that inhibits mTOR is everolimus. In some embodiments, everolimus is administered as a 0.25 mg dose orally twice daily. In some embodiments, everolimus is administered as a 0.5 mg dose orally twice daily. In some embodiments, everolimus is administered as a 0.75 mg dose orally twice daily. In some embodiments, everolimus is administered as a 1.0 mg dose orally twice daily. In some embodiments, everolimus is administered as a 1.25 mg dose orally twice daily. In some embodiments, everolimus is administered as a 1.5 mg dose orally twice daily. In some embodiments, everolimus is administered as a 1.75 mg dose orally twice daily. In some embodiments, everolimus is administered as a 2.0 mg dose orally twice daily. In some embodiments, everolimus administration begins as soon as possible after transplantation. In some embodiments, everolimus administration begins 30 days after transplantation. In some embodiments, everolimus is administered for 6 months post-transplant, 9 months post-transplant, 12 months post-transplant, 18 months post-transplant, 21 months post-transplant, or 24 months post-transplant. In some aspects, everolimus is administered for the life of the subject.

[0216] In some embodiments, the one or more additional pharmaceutically effective compounds inhibits inosine monophosphate dehydrogenase. In some embodiments, the compound that inhibits inosine monophosphate dehydrogenase is selected from a mycophenolate mofetil or a mycophenolate sodium. In some embodiments, mycophenolate mofetil is administered as a 500 mg to 1,500 mg dose orally twice daily. In some embodiments, mycophenolate mofetil is administered as a 500 mg dose orally twice daily. In some embodiments, mycophenolate mofetil is administered as a 750 mg dose orally twice daily. In some embodiments, mycophenolate mofetil is administered as a 1,000 mg dose orally twice daily. In some embodiments, mycophenolate mofetil is administered as a 1,250 mg dose orally twice daily. In some embodiments, mycophenolate mofetil is administered as a 1,500 mg dose orally twice daily. In some embodiments, mycophenolate mofetil is administered beginning on the day of administration of a T-cell depleting agent. In some embodiments, mycophenolate mofetil is administered for 6 months post-transplant, 9 months post-transplant, 12 months post-transplant, 18 months post-transplant, 21 months post-

transplant, or 24 months post-transplant. In some embodiments, mycophenolate mofetil is administered for the life of the subject. In some embodiments, mycophenolate sodium is administered as a 360 mg to 1,080 mg dose orally twice daily. In some embodiments, mycophenolate sodium is administered as a 360 mg dose orally twice daily. In some embodiments, mycophenolate sodium is administered as a 540 mg dose orally twice daily. In some embodiments, mycophenolate sodium is administered as a 720 mg dose orally twice daily beginning on the day of administration of a T-cell depleting agent. In some embodiments, mycophenolate sodium is administered as a 900 mg dose orally twice daily. In some embodiments, mycophenolate sodium is administered as a 1,080 mg dose orally twice daily. In some embodiments, mycophenolate sodium is administered beginning on the day of administration of a T-cell depleting agent. In some embodiments, mycophenolate sodium is administered for 6 months post-transplant, 9 months post-transplant, 12 months post-transplant, 18 months post-transplant, 21 months post-transplant, or 24 months post-transplant. In some embodiments, mycophenolate sodium is administered for the life of the subject.

[0217] In some embodiments, the one or more additional pharmaceutically effective compounds inhibits binding of tumor necrosis factor (TNF)-alpha to cell surface TNF receptors. In some embodiments, the compound that inhibits binding of TNF-alpha to cell TNF receptors is selected from etanercept or infliximab. In some embodiments, etanercept is administered at a dose of 50 mg to 100 mg IV on day 0 prior to transplant, and 25 mg to 50 mg SC on days 3, 7, and 10 post-transplant. In some embodiments, etanercept is administered at a dose of 100 mg IV on day 0 prior to transplant, and 50 mg SC on days 3, 7, and 10 post-transplant. In some embodiments, etanercept is administered at a dose of 50 mg IV on day 0 prior to transplant, and 25 mg SC on days 3, 7, and 10 post-transplant. In some embodiments, infliximab is administered as a 1 mg/kg IV dose to a 50 mg/kg IV dose 2 hours-pre transplant. In some embodiments, infliximab is administered as a 5 mg/kg IV dose 2 hours pre-transplant. In some embodiments, infliximab is administered as a 10 mg/kg IV dose 2 hours pre-transplant. In some embodiments, infliximab is administered as a 15 mg/kg IV dose 2 hours pre-transplant. In some embodiments, infliximab is administered as a 20 mg/kg IV dose 2 hours pre-transplant. In some embodiments, infliximab is administered as a 25 mg/kg IV dose 2 hours pre-transplant.

[0218] In some embodiments, the one or more additional pharmaceutically effective compounds is a corticosteroid. In some embodiments, the corticosteroid is selected from methylprednisolone, prednisolone, prednisone, cortisone, hydrocortisone, betamethasone, dexamethasone, or triamcinolone. In some aspects, methylprednisolone IV is administered intraoperatively according to the study center's standard of care. In some embodiments, the subject is transitioned to oral prednisone when tolerable, and the dose is tapered such that 5 mg of prednisone daily (or equivalent) is achieved by day 28 post-transplant.

[0219] In some embodiments, the present disclosure provides a method of preventing or reducing transplant rejection in a subject comprising administering to the subject in need thereof a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 20 mg/kg, wherein the method further comprises administering one or more additional pharmaceutically effective compounds selected from an anti-thymocyte globulin (ATG), a mycophenolate mofetil and/or a mycophenolate sodium, methylprednisolone, and a combination thereof, and wherein the antibody or antigen binding fragment thereof is administered at least once every 3 weeks. In some aspects, the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered on days 1, 3, 7, 14, 21, and 28 and every 21 days thereafter after transplant. In some aspects, the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered on days 1, 7, 14, 21, and 28 and every 21 days thereafter after transplant. In some aspects the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 10 mg/kg or about 20 mg/kg.

Kits and Articles of Manufacture

[0220] Further provided are kits containing the antibody or antigen binding fragments thereof described herein and instructions for use. Kits typically include a packaged combination of reagents in predetermined amounts with instructions and a label indicating the intended use of the contents of the kit. The term label or instruction includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit at any time during its manufacture, transport, sale, or

use. It can be in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of the manufacture, use or sale for administration to a human or for veterinary use. The label or instruction can also encompass advertising leaflets and brochures, packaging materials, and audio or video instructions.

Anti-CD40L Antigen Binding Molecules

[0221] In some aspects, the antibody or antigen binding fragment thereof comprises an anti-CD40 ligand antibody or antigen binding fragment thereof as known to a person of skill in the art.

[0222] In some embodiments, such antibody or antigen binding fragment thereof is MR1. In some embodiments provided herein, the antibody or antigen binding fragment thereof is a modified version of the anti-CD40L antibody hu5c8 that comprises a human IgG1 consensus framework having the variable light chain and the variable heavy chain CDR sequences of hu5c8 with an Fc domain modified to prevent platelet activation.

[0223] In some embodiments, the antibody or antigen binding fragment thereof is IDEC 131/E6040, as disclosed in U.S. Publ. Appl. No. 20010018041A1. In some embodiments, the antibody or antigen binding fragment thereof is 24-31, as disclosed in U.S. Patent No. 6,001,358A. In some embodiments, the antibody or antigen binding fragment thereof is ABI 793, as disclosed in U.S. Patent No. 7,169,389B2, In some embodiments, the antibody or antigen binding fragment thereof is ImxM90, as disclosed, e.g., in Int'l Publ. Appl. No. WO1998/039026. In some embodiments, the antibody or antigen binding fragment thereof is ImxM91, as disclosed, e.g., in Int'l Publ. Appl. No. WO1998/039026. In some embodiments, the antibody or antigen binding fragment thereof is ImxM92, as disclosed, e.g., in Int'l Publ. Appl. No. WO1998/039026.

[0224] In some embodiments, the antibody or antigen binding fragment thereof is dapirolizumab pegol, as disclosed, e.g., in U.S. Pat. No. 11,142,794B2. In some embodiments, the antibody or antigen binding fragment thereof is any one or more antibodies or antigen binding fragments thereof as disclosed in U.S. Pat. No. 8,435,514; 9,044,459; 10,106,618; 10,683,356; 11,014,990; 11,692,040; 11,384,152, in U.S. Publ. Appl. Nos. 20220380478A1, 20240059781A1, or in Int'l Publ. Appl. No. WO2023/230538 or WO2023/230526.

[0225] In some embodiments herein, the antibody or antigen binding fragment thereof is AT-1501.

[0226] In some embodiments, the antibody or antigen binding fragment thereof competitively inhibits the binding of AT-1501 to CD40 ligand. In some embodiments, the antibody or antigen binding fragment thereof competitively inhibits the binding of 5c8 to CD40 ligand. In some embodiments, the antibody or antigen binding fragment thereof competitively inhibits the binding of hu5c8 to CD40 ligand.

[0227] In some embodiments, the antibody or antigen binding fragment thereof is a modified version of the anti-CD40 ligand antibody hu5c8 that comprises a human IgG1 consensus framework having the variable light chain and the variable heavy chain CDR sequences of hu5c8 with an Fc domain modified to prevent platelet activation.

[0228] In some embodiments, the antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand. In some embodiments, the antibody or antigen binding fragment thereof comprises means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand and b) an Fc domain as described herein (see Table 4). In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand and b) an Fc domain comprising one or a combination of substitutions selected from C11S, C14S, or P23S. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand and b) an Fc domain comprising one or a combination of substitutions selected from C5S, C11S, C14S, or P23S. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked and b) an Fc domain as described herein (see Table 4). In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked and b) an Fc domain comprising one or a combination of substitutions selected from C11S, C14S, or P23S. In some embodiments, the antibody or antigen binding fragment thereof comprises a) means for binding human CD40 ligand such that the binding of CD40 ligand to CD40 is blocked and b) an Fc domain comprising one or a combination of substitutions selected from C5S, C11S,

C14S, or P23S. Examples of structures able to carry out the function of blocking CD40 ligand blocking to CD40 are described herein.

[0229] Table 4 provides a description of the SEQ ID NOs: referenced in the application.

Table 4.

SEQ ID NO	Description of Sequence
1	Heavy chain 1 (VH1)
2	Heavy chain 2 (VH2)
3	Heavy chain 3 (VH3)
4	Heavy chain 4 (VH4)
5	Light chain 1 (VL1)
6	Light chain 2 (VL2)
7	Light chain 3 (VL3)
8	Light chain 4 (VL4)
9	Heavy chain CDR1
10	Heavy chain H1 CDR2
11	Heavy chain H2 CDR2A (CDR2 and flanking region RV)
12	Heavy chain H3 CDR2B (CDR2 and flanking region RA)
13	Heavy chain H4 CDR2
14	Heavy chain H2 and H3 CDR2
15	Heavy Chain CDR3
16	Light Chain CDR1 L1 and L4
17	Light Chain CDR1 L2 and L4
18	Light Chain CDR2 L1 and L2
19	Light Chain CDR2 L3 and L4
20	Light Chain CDR3
21	Engineered effectorless IgG1 Fc with P238S and N297G mutations
22	Engineered D265A/N297A

	effectorless IgG1 constant heavy chain
23	Engineered effectorless IgG1/IgG4 hybrid constant heavy chain sequence
24	Engineered effectorless IgG4 constant heavy chain sequence
25	Constant light chain sequence
26	Heavy chain 1 (VH1) DNA
27	Heavy chain 2 (VH2) DNA
28	Heavy chain 3 (VH3) DNA
29	Heavy chain 4 (VH4) DNA
30	Light chain 1 (VL1) DNA
31	Light chain 2 (VL2) DNA
32	Light chain 3 (VL3) DNA
33	Light chain 4 (VL4) DNA
34	Fc fragment of IgG, high affinity Ia, receptor (CD64) (FCγRIa)
35	Low affinity immunoglobulin gamma Fc region acceptor IIa (FCγRIIa) (CD32)
36	low affinity immunoglobulin gamma Fc region receptor IIIa (FCγRIIIA) (CD16a)
37	Low affinity immunoglobulin gamma Fc region receptor IIIb (FCγRIIIb) (CD16b))
38	Light chain 1 with constant light chain (VL1-C)
39	Light chain 2 with constant light chain (VL2-C)
40	Light chain 3 with constant light chain (VL3-C)
41	Light chain 4 with constant light chain (VL4-C)
42	Heavy chain 1- IgG1 Fc with P238S and N297G mutations (VH1-Fc-P238/N297)
43	Heavy chain 2- IgG1 Fc with P238S and N297G mutations (VH2- Fc-P238/N297)
44	Heavy chain 3- IgG1 Fc with P238S and N297G mutations (VH3-Fc-P238/N297)
45	Heavy chain 4- IgG1 Fc with P238S and N297G mutations (VH4 – Fc-P238/N297)
46	Heavy chain 1-Fc D265A/N297A effectorless IgG1 (VH1-Fc-D265A/N297A)
47	Heavy chain 2-Fc D265A/N297A effectorless IgG1

	(VH2-Fc-D265A/N297A)
48	Heavy chain 3-Fc D265A/N297A effectorless IgG1 (VH3-Fc-D265A/N297A)
49	Heavy chain 4-Fc D265A/N297A effectorless IgG1 (VH4-Fc-D265A/N297A)
50	Heavy chain 1-Fc effectorless IgG1/IgG4 hybrid (VH1-Fc-IgG1/IgG4 hybrid)
51	Heavy chain 2-Fc effectorless IgG1/IgG4 hybrid (VH2-Fc-IgG1/IgG4 hybrid)
52	Heavy chain 3-Fc effectorless IgG1/IgG4 hybrid (VH3-Fc-IgG1/IgG4 hybrid)
53	Heavy chain 4-Fc effectorless IgG1/IgG4 hybrid (VH4-Fc-IgG1/IgG4 hybrid)
54	Heavy chain 1-Fc effectorless IgG4 constant heavy chain (VH1-Fc- IgG4)
55	Heavy chain 2-Fc effectorless IgG4 constant heavy chain (VH2-Fc- IgG4)
56	Heavy chain 3-Fc effectorless IgG4 constant heavy chain (VH3-Fc- IgG4)
57	Heavy chain 4-Fc effectorless IgG4 constant heavy chain (VH4-Fc- IgG4)
58	Light chain variable region amino acid sequence (hu5c8 and AT-1501)
59	Heavy chain variable region amino acid sequence (hu5c8 and AT-1501)
60	Fc region amino acid sequence (hu5c8)
61	AT-1501 Fc region amino acid sequence
62	AT-1501-R28K light chain variable region amino acid sequence
63	AT-1501-K74R heavy chain variable region amino acid sequence
64	AT-1501 light chain amino acid sequence
65	AT-1501 light chain nucleic acid sequence
66	AT-1501 heavy chain amino acid sequence
67	AT-1501 heavy chain nucleic acid sequence
68	AT-1501-R28K light chain amino acid sequence
69	AT-1501-R28K light chain synthetic gene nucleic acid sequence
70	AT-1501-K74R heavy chain amino acid sequence
71	AT-1501-K74R heavy chain synthetic gene nucleic acid sequence
72	CDR-1 of the AT-1501 Variable Light Chain amino acid sequence
73	CDR-2 of the AT-1501 Variable Light Chain amino acid sequence

74	CDR-2 of the AT-1501 Variable Heavy Chain amino acid sequence
75	Hu5c8 Heavy Chain amino acid sequence

[0230] One embodiment (embodiment A) is an isolated antibody that binds to CD40L and that comprises a light chain and a heavy chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94%, or at least 95%, or at least 96% or at least 97%, or at least 98% or at least 99% sequence identity with SEQ ID NO: 58 and the heavy chain comprises a variable heavy chain region and an Fc region, wherein the heavy chain variable region comprises an amino acid sequence having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity with SEQ ID NO: 59 and the Fc region comprises an amino acid sequence having at least 90%, or at least 91%, or at least 92%, or at least 93%, or at least 94%, or at least 95%, or at least 96%, or at least 97%, or at least 98%, or at least 99% sequence identity with SEQ ID NO: 60 wherein the Fc region comprises one or a combination of substitutions selected from the group consisting of C11S, C14S, and P23S.

[0231] Another embodiment (embodiment B) is an isolated antibody according to embodiment A, wherein the Fc region further comprises the amino acid substitution C5S.

[0232] In variations of the embodiments A and B, the antibody comprises a light chain variable region that does not comprise any of the substitutions T33W, S26D, and Q27E.

[0233] In other variations of embodiments A and B, the light chain variable region comprises the substitution R28K.

[0234] In some variations of the embodiments of A and B, the CDRs of the heavy and light chain have the sequences listed in Table 5.

Table 5.

CDR1 light chain	ISCRASQRVSSSTYSYMH (SEQ ID NO: 72)
CDR2 light chain	YASNLES (SEQ ID NO: 73)
CDR3 light chain	QHSWEIPPT(SEQ ID NO: 20)

CDR1 heavy chain	SYYMY (SEQ ID NO: 9)
CDR2 heavy chain	EINPSNGDTNFNEKFKS (SEQ ID NO: 74)
CDR3 heavy chain	SDGRNDMDS(SEQ ID NO: 15)

[0235] In yet other variation of embodiments A and B, the light chain variable region comprises the amino acid sequence ICRRASQRVSSSTYSYMH (SEQ ID NO: 72). In still other embodiments, the light chain variable region comprises the amino acid sequence ICRRASQRVSSSTYSYMH (SEQ ID NO: 72) and one or both of the amino acid sequences YASNLES (SEQ ID NO: 73) and QHSWEIPPT (SEQ ID NO: 20).

[0236] In some variations of embodiments A and B, the light chain variable region comprises the amino acid sequence of SEQ ID NO: 58. In yet other embodiments the light chain variable region consists of the amino acid of SEQ ID NO: 58. In some embodiments, the light chain consists essentially of the amino acid sequence of SEQ ID NO: 64. In other embodiments, the light chain consists of the amino acid sequence of SEQ ID NO: 64. In still other embodiments, the light chain comprises the amino acid sequence of SEQ ID NO: 68. In yet other embodiments, the light chain consists essentially of the amino acid sequence of SEQ ID NO: 68. In still other embodiments, the light chain consists of the amino acid sequence of SEQ ID NO: 68.

[0237] In other variations of the embodiments A and B, the antibody comprises a heavy chain variable region that does not comprise any of the substitutions T30H, Y33W, or S54N. In some embodiments of the antibodies of embodiments A and B, the light chain variable region does not comprise any of the substitutions T33W, S26D, and Q27E. In other variations of embodiments A and B, the light chain variable region does not comprise any of the substitutions T33W, S26D, and Q27E and the heavy chain variable region does not comprise any of the substitutions T30H, Y33W, or S54N.

[0238] In yet other variations of the embodiments A and B, the heavy chain variable region comprises the substitution K74R. In one embodiment the heavy chain variable region comprises one or any combination of the amino acid sequences SYYMY (SEQ ID NO: 9), EINPSNGDTNFNEKFKS (SEQ ID NO: 74), and SDGRNDMDS (SEQ ID NO: 15).

[0239] In another embodiment, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 59. In yet another embodiment the heavy chain variable

region consists essentially of the amino acid sequence of SEQ ID NO: 59. In still another embodiment the heavy chain variable region consists of the amino acid sequence of SEQ ID NO: 59. In some embodiments, the heavy chain variable region comprises the amino acid sequence of SEQ ID NO: 63. In yet other embodiments the heavy chain variable region consists essentially of the amino acid sequence of SEQ ID NO: 63. In still other embodiments the heavy chain variable region consists of the amino acid sequence of SEQ ID NO: 63.

[0240] Some embodiments provided herein relate to an isolated antibody, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 58 and the heavy chain consists of the amino acid sequence of SEQ ID NO: 66.

[0241] Some embodiments provided herein relate to an isolated antibody, wherein the light chain consists of the amino acid sequence of SEQ ID NO: 64 and the heavy chain consists of the amino acid sequence of SEQ ID NO: 66.

[0242] Some embodiments provided herein relate to an isolated antibody wherein the light chain variable region comprises the amino acid sequence of SEQ ID NO: 62 and the heavy chain consists of the amino acid sequence of SEQ ID NO:66.

[0243] Still another embodiment is an isolated antibody wherein the light chain consists of the amino acid sequence of SEQ ID NO: 68 and the heavy chain consists of the amino acid sequence of SEQ ID NO: 66.

[0244] Yet another embodiment, is an isolated antibody wherein the light chain consists of the amino acid sequence of SEQ ID NO: 64 and the heavy chain consists of the amino acid sequence of SEQ ID NO: 70.

[0245] Another embodiment is an isolated antibody wherein the light chain consists of the amino acid sequence of SEQ ID NO: 68 and the heavy chain consists of the amino acid sequence of SEQ ID NO: 70.

[0246] In some embodiments of the present disclosure provided herein relate to an isolated antibody or antigen binding fragment thereof, wherein the light chain comprises an amino acid sequence disclosed in Table 4 and the heavy chain comprise an amino acid sequence disclosed in Table 4. In some embodiments of the present disclosure provided herein relate to an isolated antibody or antigen binding fragment thereof, wherein the light chain comprises a light chain variable amino acid sequence disclosed in Table 4 and the heavy chain comprise a heavy chain variable amino acid sequence disclosed in Table 4. In some embodiments, the antibody or antigen binding

fragment thereof competitively inhibits the binding of an antibody or antigen binding fragment thereof, wherein the light chain comprises an amino acid sequence disclosed in Table 4 and the heavy chain comprise an amino acid sequence disclosed in Table 4, to CD40 ligand. In some embodiments, the antibody or antigen binding fragment thereof competitively inhibits the binding of an antibody or antigen binding fragment thereof, wherein the light chain comprises a light chain variable amino acid sequence disclosed in Table 4 and the heavy chain comprise a heavy chain variable amino acid sequence disclosed in Table 4, to CD40 ligand.

[0247] Some embodiments of the present disclosure relate to modifying biomarkers in a subject with treatment of a compound targeting CD40/CD40L. In some embodiments, the biomarker is a protein involved in CD40/CD40L activity. In some embodiments, the biomarker is CD40. In some embodiments, the biomarker is CD40L. In some embodiments, the biomarker is NFL. In some embodiments, the biomarker is a pro- inflammatory marker, or linked to inflammation. In some embodiments, the biomarker is a cytokine and/or an interleukin. In some embodiments, the biomarker is one or more of IgA, IgE, CD40L, C3, CXCL9, CXCL10, and/or IgM.

[0248] In some embodiments, treatment with a compound that blocks the interaction between CD40 and CD40 ligand, such as an antibody or antigen binding fragment thereof that specifically binds CD40 ligand or an antibody or antigen binding fragment thereof that specifically binds CD40 increases the concentration of one or more biomarkers. In some embodiments, treatment with a compound that blocks the interaction between CD40 and CD40 ligand, such as an antibody or antigen binding fragment thereof that specifically binds CD40 ligand or an antibody or antigen binding fragment thereof that specifically binds CD40 decreases the concentration of one or more biomarkers. In some embodiments, treatment with a compound that blocks the interaction between CD40 and CD40 ligand, such as an antibody or antigen binding fragment thereof that specifically binds CD40 ligand or an antibody or antigen binding fragment thereof that specifically binds CD40 increases at least one biomarker concentration, and decreases at least one other biomarker concentration. In some embodiments, the baseline levels of the at least one biomarker serve as a predictor for the response of a subject with a kidney-related disease, disorder, or condition to treatment with a compound that blocks the interaction between CD40 and CD40 ligand, such as an antibody or antigen binding fragment thereof that specifically binds

CD40 ligand or an antibody or antigen binding fragment thereof that specifically binds CD40.

ENUMERATED EMBODIMENTS

[0249] Embodiment 1. A method of preventing or reducing transplant rejection in a subject, the method comprising: selecting a subject having or in need of having a transplant; administering a therapeutically effective dose of a compound against CD40L or CD40 to the subject prior to, during, or after transplantation, the compound comprising an anti-CD40L antibody or an anti-CD40 antibody; and preventing or reducing transplant rejection.

[0250] Embodiment 2. The method of Embodiment 1, wherein the subject is mammalian and/or human.

[0251] Embodiment 3. The method of Embodiments 1 or 2, wherein the compound blocks the interaction between CD40 and CD40L.

[0252] Embodiment 4. The method of any one of Embodiments 1-3, wherein the compound is AT-1501.

[0253] Embodiment 5. The method of any one of Embodiments 1-4, wherein the compound is administered at least once every three weeks.

[0254] Embodiment 6. The method of any one of Embodiments 1-5, wherein the compound is administered at a dose of between 200 mg/kg and 100 mg/kg; preferably at a dose between 1 mg/kg and 20 mg/kg.

[0255] Embodiment 7. The method of any one of Embodiments 1-6, wherein the transplant is a tissue transplant, cell transplant, or organ transplant.

[0256] Embodiment 8. The method of any one of Embodiments 1-7, wherein the transplant is a xenograft, allograft, or autograft.

[0257] Embodiment 9. The method of any one of Embodiments 1-8, wherein the transplant is a heart transplant, lung transplant, liver transplant, kidney transplant, islet cell transplant, cornea transplant, trachea transplant, or skin transplant.

[0258] Embodiment 10. The method of any one of Embodiments 1-9, wherein the transplant is a kidney transplant.

[0259] Embodiment 11. The method of any one of Embodiments 1-9, wherein the transplant is a pancreatic islet cell transplant.

[0260] Embodiment 12. The method of any one of Embodiments 1-11, wherein the subject suffers from a disease or disorder.

[0261] Embodiment 13. The method of Embodiment 12, wherein the disease or disorder is an autoimmune disease, wherein the autoimmune disease is systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, or Graves' disease.

[0262] Embodiment 14. The method of any one of Embodiments 1-13, the method further comprising administering a second pharmaceutically effective compound.

[0263] Embodiment 15. The method of Embodiment 14, wherein the second compound blocks the interaction between CD28 and CD86 or between CD28 and CD80.

[0264] Embodiment 16. The method of Embodiment 14, wherein the second compound targets at least one of the biomarkers selected from the group consisting of: interleukins, cytokines, and proinflammatory markers.

[0265] Embodiment 17. The method of Embodiment 14, wherein the second compound is a CTLA4-Ig fusion protein, an abatacept, a belatacept, or a galiximab.

[0266] Embodiment 18. The method of any one of Embodiments 1-17, wherein the compound is administered orally, parenterally, or topically.

[0267] Embodiment 19. The method of Embodiment 18, wherein the compound is administered parenterally.

[0268] Embodiment 20. The method of Embodiment 19, wherein the compound is administered by injection, most preferably intravenous, intramuscular, or subcutaneous injection.

[0269] Embodiment 21. The method of any one of Embodiments 1-20, wherein the compound that targets CD40L or CD40 is an antibody that comprises: a heavy chain variable region (VH) comprising: a CDRH1 domain comprising the sequence set forth in SEQ ID NO: 66; a CDRH2 domain comprising the sequence set forth in SEQ ID NO: 67, 68, 69, 70, or 71; and a CDRH3 domain comprising the sequence set forth in SEQ ID NO: 72; and a light chain variable region (VL) comprising: a CDRL1 domain comprising the sequence set forth in SEQ ID NO: 73 or 20; a CDRL2 domain comprising the sequence set forth in SEQ ID NO: 9 or 74; and a CDRL3 domain comprising the sequence set forth in SEQ ID NO: 15.

[0270] Embodiment 22. The method of any one of Embodiments 1-21, wherein the compound that targets CD40L or CD40 is an antibody that comprises: a heavy chain variable region (VH) having the amino acid sequence as set forth in SEQ ID NOs: 58, 59, 60, or 61; and a light chain variable region (VL) having the amino acid sequence as set forth in SEQ ID NOs: 62, 63, 64, or 65.

[0271] Embodiment 23. The method of any one of Embodiments 1-22, wherein the method improves the kidney function as measured by aggregate mean estimated glomerular filtration rate (eGFR).

[0272] Embodiment 24. The method of Embodiment 23, wherein the eGFR is at least 50 mL/min/1.73 m^2 after 90 days following the administering.

[0273] Embodiment 25. The method of Embodiment 23, wherein the eGFR is at least 75 mL/min/1.73 m^2 after 90 days following the administering.

[0274] Embodiment 26. The method of Embodiment 23, wherein the eGFR is at least 90 mL/min/1.73 m^2 after 1 year following the administering.

[0275] Embodiment 27. The method of any one of Embodiments 1-26, further comprising restoring kidney function to a normal level following kidney transplant or kidney damage as measured by eGFR.

EXAMPLES

[0276] Embodiments are further defined in the following Examples. It should be understood that these Examples are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics, and without departing from the spirit and scope thereof, can make various changes and modifications of the embodiments to adapt it to various usages and conditions. Thus, various modifications of the embodiments, in addition to those shown and described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. The disclosure of each reference set forth herein is incorporated herein by reference in its entirety, and for the disclosure referenced herein.

EXAMPLE 1

A Phase 2a, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of AT-1501 in Patients with IgA Nephropathy

[0277] Four human subjects with IgAN (Berger's Disease) were given kidney transplants and monitored for a period of 12 weeks. At the end of those twelve weeks, a urine sample was collected from each subject. These samples were then screened for changes in proinflammatory markers, compared to levels in each subject's urine prior to the kidney transplant.

[0278] The IgAN-correlated proinflammatory markers IgA, IgE, CD40L, and C3 noticeably decreased in patients after 12 weeks (FIGs. 14A-14D). Furthermore, the general transplant proinflammatory markers CXCL9, CXCL10, IgM, and C3 decreased after 12 weeks (FIGs. 15A-15D). Given the strong decrease in CD40L and CD40L-correlated proteins in subjects upon transplanting with a healthy kidney, it appears likely that subsequent treatment with CD40L targeting compounds such as those disclosed herein may help accelerate recovery and the reduction of inflammation in subjects.

EXAMPLE 2

A Phase 1b, Multicenter, Open Label Study to Evaluate the Safety, Pharmacokinetics and Efficacy of AT-1501 in Patients Undergoing Kidney Transplant

Initial Phase 1B Human Clinical Trials

[0279] More than 40,000 people receive a kidney transplant annually in the United States. Twenty-five years ago, the calcineurin inhibitor (CNI), tacrolimus, in conjunction with standard polypharmacy regimens, was shown to reduce cellular and antibody mediated rejection, improving short-term outcomes for transplant recipients and making transplant a more viable option for patients in need of an organ transplant. Indeed, kidney transplant survival at 12 months post-transplant is greater than 90%. Although tacrolimus has had a dramatic impact on 1-year survival rates for organ transplant, long-term survival rates (> 3 years) have not changed since its introduction, suggesting that further improvements are needed.

[0280] CD40L is a costimulatory type II transmembrane receptor for CD40, as shown in FIG. 17. Binding of CD40L on T helper cells to CD40 on antigen-presenting cells induces multiple downstream immune and inflammatory responses. These include B and T cell clonal expansion; antibody production, class-switching, and maturation; and pro-inflammatory cytokine and chemokine production. Tegoprubart (AT-1501) is a humanized IgG1, kappa monoclonal antibody that blocks CD40L (CD154, gp39) binding to CD40.

[0281] Historical studies over the last 30 years have shown that costimulatory inhibition is an effective strategy for the prevention of transplant rejection in nonhuman primates. These studies suggest the inhibition of CD40L is more effective at preventing transplant rejection than tacrolimus and more effective than the inhibition of other costimulatory signaling pathways.

[0282] Tegoprubart has been shown effective in the prevention of cellular and antibody mediated rejection in nonhuman primates and is currently being studied in kidney transplant recipients. Tegoprubart evaluated in this example to determine whether it can safely prevent kidney transplant rejection and superior graft function as compared to current standard of care with tacrolimus.

[0283] This example demonstrates use of tegoprubart in the prevention of transplant rejection for adults undergoing a de novo kidney transplant procedure at five transplant centers in Canada, Australia, and the United Kingdom. The clinical trial is a 52-week, open label, single dose level study of adult participants receiving a kidney transplantation from either a living or deceased donor.

[0284] Participants are eligible for consideration for the study only if all of the following criteria are met at the time of screening:

1. Male or female $\geq$ 18 years of age.
2. Recipient of their first kidney transplant from a living or deceased donor.
3. Willing and able to comply with the study requirements including prohibited concomitant medication restrictions.
4. Agree not to participate in another interventional study while on treatment.
5. Willing and able to comply with contraception requirements during and for at least 90 days after the last administration of study drug.

[0285] Participants are excluded from the study if any of the following criteria applied at the time of screening:

1. Induction therapy, other than study assigned rATG, planned as part of initial immunosuppressive regimen.
2. Currently treated with any systemic immunosuppressive regimen, including immunologic biologic therapies, with the exception of 5 mg prednisone or equivalent daily.
3. Previous treatment with AT-1501 or any other anti-CD40L therapy.
4. The participant has previously received a bone marrow transplant or any other solid organ transplant, including a kidney, or will be undergoing a multi organ or dual kidney transplant.
5. Will receive a kidney with an anticipated cold ischemia time of > 30 hours.
6. Will receive a kidney from a living donor who is age ≥ 65 years, or will receive a kidney from a deceased donor that meets any of the following criteria:
    a. Donation after Cardiac Death (DCD) criteria; or
    b. Extended Criteria Donor (ECD) criteria, defined as:
        i. Is blood group (ABO) incompatible; or
        ii. Age ≥ 60 years; or
        iii. Age 50-59 years with any 2 of the following criteria
            1. Death due to cerebrovascular accident
            2. History of hypertension
            3. Terminal creatinine ≥ 133 μmol/L (1.5 mg/dL).
7. Human leukocyte antigen identical (two haplotype match or zero HLA mismatch) donor.
8. History of any other acute or chronic medical condition or pre-planned medical/surgical procedure that, in the opinion of the Investigator, would comprise the safety of the patient or the integrity of study results.
9. Medical conditions that require chronic use of systemic steroids at a dose higher than 5 mg prednisone or equivalent per day.
10. History of a thromboembolic event (TE), known hypercoagulable state, or condition requiring long term anticoagulation:
    a. Patients with a history of clotted venous access not requiring long-term anticoagulation may be included at the Investigator's discretion if have no other history of TE events or known hypercoagulable state;

b. Participants with no history of TE, treated with low dose aspirin or receiving anticoagulation therapy as prophylaxis will not be excluded.

11. Recipient or donor is known to be seropositive for human immunodeficiency virus (HIV), hepatitis C virus (HCV), nucleic acid testing (NAT) and/or antibody [note that for recipients or donor known to have been successfully treated for HCV, a positive antibody test is not exclusionary provided there is a negative NAT], hepatitis B virus (HBV) surface antigen (HBsAg), or HBV core antibody (HBcAb).
12. Current calculated panel reactive antibody (cPRA) > 80%.
13. Current malignancy or a history of malignancy (within the past 5 years), except nonmetastatic basal or squamous cell carcinoma of the skin that has been treated successfully.
14. Significant liver disease, defined as having elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels greater than 2 times the upper value of the normal range of the study center and impaired liver function.
15. Current or history of active tuberculosis infection. Laboratory evidence of infection (positive purified protein derivative [PPD] test or QuantiFERON TB-Gold) in the absence of clinical infection is exclusionary unless the patient has completed treatment as recommended by local authorities:
    a. Patients with documented Bacille Calmette-Guerin (BCG) vaccination and a negative chest x-ray may be included at the Investigator's discretion.
16. Concurrent participation in another interventional study or treatment with an investigational drug up to 30 days or 5 half-lives (depending on medication) prior to screening.
17. Treatment with an immunologic biologic compound (i.e., tumor necrosis factor inhibitors, [e.g., etanercept, adalimumab], intravenous immunoglobulin [IVIg]) within 90 days of Screening.
18. Known hypersensitivity to mycophenolate, rATG, corticosteroids, or any of their components.
19. Any form of substance abuse, psychiatric disorder, or a condition that, in the opinion of the Investigator, could invalidate communication with the Investigator.
20. Clinically significant abnormal ECG at screening.
21. Recipient is seronegative for Epstein-Barr Virus (EBV) at screening.

22. Recipient has a positive polymerase chain reaction (PCR) or antigen test for Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at screening (a positive SARS-CoV-2 test for the donor does not exclude a patient from enrollment - Investigator to consult with Medical Monitor).
23. Positive T- or B-cell crossmatch that is due to HLA antibodies.
24. Presence of a donor-specific antigen at screening.
25. Thrombocytopenia (platelets < 75,000 per mm3 / 75×109/L), leukopenia (white blood cells [WBC] < 3,000 per mm^3 / 3×109/L), or anemia (hemoglobin < 8 g/dL / 80 g/L) at screening.
26. Desensitization therapy within 6 months of transplant.
27. Pregnancy or breastfeeding.
28. Unlikely to comply with the visits scheduled in the protocol, in the opinion of the Investigator.
29. Any vaccination within 30 days prior to transplant and planned vaccination less than 3 months post-transplant.
30. [UK only]: Hypersensitivity to rabbit proteins and known sensitivity to ingredients in AT-1501.
31. [UK only]: Patients that received a deceased donor kidney that qualifies as a rapid action or fast track allograft under the UK's Kidney Fast Track offering scheme.

[0286] The participants are administered an immunosuppressive regimen using ATG induction therapy plus CNI free maintenance therapy, including mycophenolate, corticosteroids, and tegoprubart as a replacement for tacrolimus. The drugs are administered as follows.

[0287] The first four participants selected for the trial were two females and two males, ages 60-77, with baseline characteristics as shown in Table 6 below. Donor characteristics are also provided in Table 6.

Table 6.

Participants	1	2	3	4
Age (years)	60	77	62	68
Gender	Female	Female	Male	Male
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian

Height (cm)	165	161	191	
Weight (kg); BMI	62; 23	61; 24	87; 24	
Underlying Condition	Polycystic kidney disease	Type 1 diabetes	Polycystic kidney disease	Type 1 diabetes
Dialysis	No	Yes	No	Yes
Donor Type	Living	Deceased	Living	Living
Donor Information				
Age	40	42	55	57
Gender	Male	Female	Female	Male
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian
Height (cm)	182	160	160	175
Weight (kg); BMI	113; 34	68; 27	65; 25	81; 26.4
Cause of Death		Brain dead secondary to hypoxia		
Cold Ischemia Time (hours)	3.24	14.4	3.51	3.3

[0288] These four participants each underwent a kidney transplant. These participants received rabbit anti-thymocyte globulin (rATG) 1.5 mg/kg/dose IV for 4 doses (total of 6 mg/kg). The first dose was started prior to revascularization and the remaining 3 doses (total 4.5 mg/kg) were within 5-10 days post-transplant consistent with labeled instructions. These participants received a corticosteroid per standard of care, to be tapered to 5 mg prednisone daily (or equivalent) by 28 days post-transplant. These participants received mycophenolate mofetil 1000 mg BID or mycophenolate sodium 720 mg BID. These participants received tegoprubart 20 mg/kg via IV infusion on Days 1, 3, 7, 14, 21, 28 and every 21 days thereafter.

[0289] Kidney function for these four participants was monitored for the next 120 days using the estimated glomerular filtration rate (eGFR), as shown in Table 7 below (wherein an "*" represents data with a p value between 0.05 and 0.01; an "**"

represents data with a p value between 0.01 and 0.001; an "***" represents data with a p value that is less than 0.001) and FIG. 16.

Table 7.

	Baseline	Week 4	Week 12	Week 24	Week 36
Subject 1	9	96	96	80	77***
Subject 2	10	85	79	85**	
Subject 3	12	49	54*		
Subject 4	9	88			
Mean	10	77	76	82	

[0290] Tegoprubart was administered at four different times, as shown in FIG. 16. Graft function measured using eGFR at 12 months post transplant is associated independently with subsequent death-censored graft failure. Of multiple covariates, 12-month eGFR is the strongest predictor of graft failure. Thus far, kidney function has been greatly enhanced with a low hazard ratio.

[0291] All participants received a total dose of 6 mg of rabbit anti-thymocyte globulin (rATG) starting on the day of transplant through the first 10 days after transplant. Participants received corticosteroids starting on the day of transplant tapering to a 5 mg dose by day 28 after transplant. Participants received 1000 or 720 mg twice a day (BID) mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant. Participants received 20 mg/kg of tegoprubart via IV infusion weekly until day 28 followed by infusions every 21 days (Fig. 32).

[0292] The baseline characteristics of thirteen participants are outlined in FIG. 20. Participants received a total dose of 6 mg/kg of rATG starting on the day of transplant through the first 10 days after transplant. All participants receive corticosteroids starting on the day of transplant, tapering to a 5 mg prednisone daily dose (or equivalent) by day 28 after transplant. Participants received 1000 or 720 mg twice a day (BID) mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant. Participants received 20 mg/kg of tegoprubart via IV infusion weekly until day 28 followed by infusions every 21 days thereafter (FIG. 23). Participants were treated for one year, after which time they had the option of continuing tegoprubart in an extension study.

[0293] The primary endpoints are to assess the safety and tolerability of tegoprubart and to characterize the pharmacokinetic profile of tegoprubart. Other endpoints include characterizing the pharmacodynamics of tegoprubart, the incidence of biopsy proven rejection (BPAR), changes in estimated glomerular filtration rate (eGFR), and exploratory biomarkers including donor derived cell free DNA, donor-specific antibodies, CD40L receptor occupancy, gene expression studies, blood and urine cytokine/chemokine/inflammatory marker studies.

[0294] The results of this example demonstrate that tegoprubart is safe and well tolerated in patients undergoing de novo kidney transplantation. The aggregate mean eGFR was greater than or equal to 60 mL/min/1.73 m^2 starting thirty days post transplant, as shown in FIGs. 22A-22B. The mean eGFR values are shown in Table 8.

Table 8.

Days After Transplantation	Mean eGFR (mL/min/1.73 m^2) (FIG.22A)	Mean eGFR (mL/min/1.73 m^2) (FIG. 22B)
0	19.30	19.69
30	67.75	70.36
90	65.96	69.13
150	60.30	63.51
210	67.43	70.74
270	63.91	75.07
330	73.91	82.21
390	94.05	94.05

[0295] There have been no reports of donor-specific antibodies (DSA). There have been 4 cases of Polyomavirus viremia and viral titers have been well managed with transient reductions in immunosuppressive medications as per standard of care. There have been no cases of BK nephropathy. There have been no cases of CMV infection, hyperglycemia, new onset diabetes, ortremors (FIG. 21).

[0296] One patient experienced a T cell-mediated rejection (Banff score 1a) on day 99 based on local pathology. The patient was treated and remains in the study. One participant discontinued the study on day 217 due to alopecia and fatigue. One

participant discontinued the study on day 54 due to Polyomavirus viremia, and one participant discontinued the study on day 176 due to transplant rejection (Banff score 2B). One participant was excluded from the mean eGFR curve shown in FIG. 22B due to a surgical complication (acute tubular necrosis (ATN)), which results in a lack of blood flow to the kidney, and which occurred during surgery on day 0, prior to and unrelated to administration of the study drug. The patient remains in the study. BK infections were all controlled by temporarily decreasing immunosuppression and CMV infections both controlled by antivirals.

[0297] These data show that tegoprubart is effective in the prevention of kidney transplant rejection, and also show that following kidney transplant, kidney function may be restored to normal levels. For example, the aggregate mean eGFR for several subjects was above 70 mL/min/1.73 m^2 for all reported time points after day 90. Thus, these data unexpectedly show that the methods described herein restored kidney function following kidney transplant to normal levels. In particular, the aggregate mean eGFR after one year was greater than 90 mL/min/1.73 m^2 (91 mL/min/1.73 m^2) (FIGs. 22A-22B) for several subjects as well. This was unexpected because this level is almost twice that when using standard care treatment, and shows that the methods described herein unexpectedly improve kidney function to levels greater than those obtained using standard care methods.

[0298] The individual patient eGFR levels are as shown in FIG. 25. As can be seen, the average patient had significantly higher eGFR compared with the estimated concentration of mean eGFR from treatments with tacrolimus (tac), the current standard of care. This also correlates with the higher survival following kidney transplant in anti-CD40 and anti-CD40L treatments compared with tac treatment (FIG. 24).

[0299] As shown above, the aggregate mean estimated glomerular filtration rate (eGFR) – a measure of kidney function – measured above 60 mL/min/1.73 m^2 at all reported time points after day 30. Two subjects completed 12 months on therapy post-transplant and both demonstrated mean eGFRs above 90 mL/min/1.73 m^2 at day 390. Historical studies using standard of care immunosuppression therapy have reported average eGFRs generally in the low 50 mL/min/1.73 m^2 range during the first year after kidney transplant. To date, three subjects discontinued the study because of hair

loss and fatigue, viral infection, or rejection. There have been no cases of graft loss or death.

Updated Phase 1B Human Clinical Trials

[0300] All participants receive 1.0 to 1.5 mg/kg/day IV (for a maximum of 4.5 mg/kg) of rabbit anti-thymocyte globulin (rATG) starting on the day of transplant, and the remaining doses are administered within 5-10 days post-transplant consistent with the labeled instructions. All participants receive corticosteroids (methylprednisolone IV) starting on the day of transplant, according to the study center's standard of care, tapering to a 5 mg prednisone daily dose (or equivalent) by day 28 after transplant.

[0301] Participants in Cohort 1 receive 20 mg/kg of tegoprubart via IV infusion on days 1, 7, 14, 21, 28 and every 21 days thereafter. Participants also receive 1000 mg or 720 mg twice a day (BID) mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant.

[0302] Participants in Cohort 2 receive 10 mg/kg of tegoprubart via IV infusion on days 1, 3, 7, 14, 21, 28 and every 21 days thereafter. Participants also receive 1000 or 720 mg twice a day (BID) mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant.

[0303] Participants in Cohort 3 receive 20 mg/kg of tegroprubart via IV infusion on days 1, 3, 7, 14, 21, 28 and every 21 days thereafter. Participants receive 500 or 360 mg twice a day (BID) mycophenolate mofetil or mycophenolate sodium respectively starting on day of transplant.

[0304] Donor characteristics are also provided in Table 9, which includes data for the first four participants identified in Table 6.

Table 9.

Participant	Age	Gender	Ethnicity	Disease	Donor	Donor Age	Donor Sex	Donor Race	Cold Ischemia (Hours)	Donor:Recipient Blood Type	HLA Total Match	Donor:Recipient CMV IgG
1	60	F	C	PCKD	LD	40	M	W	3.24	O:O	5	D-/R-
2	77	F	C	DKD	DD	42	F	W	14.4	B:B	5	D-/R+
3	62	M	C	PCKD	LD	55	F	W	3.51	A:A	4	D+/R-
4	68	M	C	DKD	LD	57	M	W	3.3	O:O	4	D-/R-
5	23	F	C	GN	LD	49	F	A	3.41	A:A	2	D+/R+
6	44	M	C	PCKD	DD	42	F	W	12.12	O:O	4	D-/R+
7	65	M	C	DKD	LD	64	F	W	3.07	A:A	2	D+/R+
8	57	F	C	DKD	LD	45	F	W	3.48	A:A	6	D+/R+
9	35	M	C	GN	LD	59	M	O	4.45	O:O	5	D+/R+
10	56	F	C	PCKD	LD	54	F	W	4.15	O:O	4	D-/R+
11	59	M	C	DKD	LD	63	F	W	3.56	B:B	6	D+/R+
12	38	M	A	FSGS	DD	32	F	NA	7.15	A:A	5	D+/R+
13	68	M	AL	DKD	DD	38	F	W		A:A	5	D+/R+
14	61	M	C	GN	LD	52	M	W	4.0	A:A	6	D-/R-
15	49	M	A	UNK atrophy	LD	59	M	W	5.07	O:O	5	D+/R-
16	51	F	L	GN	DD	41	F	W	12.45	O:O	3	D-/R+
17	51	F	C	HT	LD	49	F	W	4.55	A:A	6	D-/R+
18	61	M	C	GN	LD	26	F	W	3.5	A:A	5	D-/R-
19	72	M	C	GN	LD	60	M		10.03	O:O		D+/R-

Ethnicity: Caucasian (C), Asian (A), Alaskian (AL), Latino (L); Donor: Living Donor (LD), Deceased Donor (DD); Donor Race: White (W), Asian (A), Other (O), Not Attributed (NA); Disease: Polycystic kidney disease (PCKD), Diabetic kidney disease (DKD), Glomerulonephritis (GN), Focal Segmental Glomerulosclerosis (FSGS), Unilateral Kidney Atrophy (UNK Atrophy)

[0305] These additional data show that tegoprubart is effective in the prevention of kidney transplant rejection, and also show that following kidney transplant, kidney function may be restored to normal levels. FIG. 27. The aggregate mean eGFR was above 60 mL/min/1.73 m^2 for all reported time points after day 90 and sustained through day 360. Thus, these data unexpectedly show that the methods described herein restored kidney function following kidney transplant to levels above 60 mL/min/1.73 m^2, which is well above standard of care tacrolimus.

EXAMPLE 3

BESTOW: A Phase 2, Multicenter, Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Tegoprubart in Patients Undergoing Kidney Transplantation

[0306] This example demonstrates use of tegoprubart in the prevention of transplant rejection for adults undergoing a de novo kidney transplant procedure at transplant centers in the United States and other countries, including Australia, Brazil, Canada, France, Germany, and Spain. The clinical trial is a 52-week, head-to-head superiority study of adult participants receiving a kidney transplantation from either a living or deceased donor.

[0307] Participants will receive ATG induction therapy plus either tegoprubart or the active comparator, tacrolimus, as part of a maintenance immunosuppressive regimen including mycophenolate and a corticosteroid taper.

[0308] Participants are eligible for consideration of the study only if all of the following criteria applied at the time of screening:

1. Male or female ≥ 18 years of age.
2. Recipient of their first kidney transplant from a living or deceased donor.
3. Agree to comply with contraception requirements during and for at least 90 days after the last administration of study drug.

[0309] Participants are excluded from the study if any of the following criteria applied at the time of screening:

1. Induction therapy, other than study assigned rATG, planned as part of initial immunosuppressive regimen.
2. Currently treated with any systemic immunosuppressive regimen, including immunologic biologic therapies.

3. Currently treated with corticosteroids other than topical or inhaled corticosteroids.
4. Will receive a kidney with an anticipated cold ischemia time of > 30 hours.
5. Will receive a kidney from a donor that meets any of the following:
   a. Donation after Cardiac Death (DCD) criteria; or
   b. Kidney Donor Profile Index (KDPI) of > 85%; or
   c. Is blood group (ABO) incompatible.
6. Medical conditions that require chronic use of systemic corticosteroids or other immunosuppressants.
7. History of a thromboembolic event, known hypercoagulable state, or condition requiring long-term anticoagulation.
8. Positive T- or B-cell crossmatch that is due to HLA antibodies or presence of a DSA at screening.

[0310] The primary endpoints are graft function, as measured by eGFR, and safety and tolerability of tegoprubart. Secondary endpoints include participant and graft survival, BPAR, immune cell infiltrate of graft biopsy, rate of new onset diabetes mellitus (NODAT), and biomarker measures of kidney injury and rejection risk.

WHAT IS CLAIMED IS:

1. A method of improving transplanted kidney function in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the transplanted kidney function is measured by an aggregate mean estimated glomerular filtration rate (eGFR) and is improved relative to a control.

2. The method of claim 1, wherein the control is a kidney transplant under the standard of care of tacrolimus.

3. The method of claim 2, wherein the improvement of eGFR is by at least or about 10% relative to a kidney transplant under the standard of care of tacrolimus.

4. The method of claim 2 or 3, wherein the improvement of eGFR is by at least or about 20% relative to a kidney transplant under the standard of care of tacrolimus.

5. The method of claim 2, wherein the improvement of eGFR is an increase by at least 5 mL/min/1.73 m^2 relative to a kidney transplant under the standard of care of tacrolimus.

6. The method of claim 2 or 5, wherein the improvement of eGFR is an increase by at least 10 mL/min/1.73 m^2 relative to a kidney transplant under the standard of care of tacrolimus.

7. The method of claim 2 or 5, wherein the improvement of eGFR is an increase by at least 15 mL/min/1.73 m^2 relative to a kidney transplant under the standard of care of tacrolimus.

8. The method of any one of claims 1, 2 or 5-7, wherein the improvement of eGFR is to at least 50 mL/min/1.73 m^2 after 90 days following the administering.

9. The method of any one of claims 1, 2 or 5-8, wherein the improvement of eGFR is to at least 60 mL/min/1.73 m^2 after 90 days following the administering.

10. The method of any one of claims 1, 2 or 5-9, wherein the improvement of eGFR is to at least 70 mL/min/1.73 m^2 after 90 days following the administering.

11. The method any one of claims 1, 2 or 5-10, wherein the improvement of eGFR is to at least 80 mL/min/1.73 m^2 after 90 days following the administering.

12. The method of any one of claims 1, 2 or 5-11, wherein the improvement of eGFR is to at least 50 mL/min/1.73 m^2 after 1 year following the administering.

13. The method of any one of claims 1, 2 or 5-12, wherein the improvement of eGFR is to at least 60 mL/min/1.73 m^2 after 1 year following the administering.

14. The method of any one of claims 1, 2 or 5-13, wherein the improvement of eGFR is to at least 70 mL/min/1.73 m^2 after 1 year following the administering.

15. The method of any one of claims 1, 2 or 5-14, wherein the improvement of eGFR is to at least 80 mL/min/1.73 m^2 after 1 year following the administering.

16. The method of any one of claims 1, 2 or 5-15, wherein the improvement of eGFR is to at least 90 mL/min/1.73 m^2 after 1 year following the administering.

17. The method of any one of claims 1-16, further comprising restoring kidney function to a normal level following kidney transplant as measured by eGFR.

18. A method of preventing or reducing kidney transplant rejection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the method prevents or reduces kidney transplant rejection in the subject for greater than a year after transplant as measured by an aggregate mean estimated glomerular filtration rate (eGFR).

19. The method of claim 18, wherein the eGFR greater than a year after transplant is at least 50 mL/min/1.73 m^2.

20. The method of claim 19, wherein the eGFR greater than a year after transplant is at least 60 mL/min/1.73 m^2.

21. The method of claim 19 or 20, wherein the eGFR greater than a year after transplant is at least 70 mL/min/1.73 m^2.

22. The method of any one of claims 19-21, wherein the eGFR greater than a year after transplant is at least 80 mL/min/1.73 m^2.

23. The method of any one of claims 19-22, wherein the eGFR greater than a year after transplant is at least 90 mL/min/1.73 m^2.

24. A method of delaying kidney transplant rejection in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the delaying kidney transplant rejection is relative to a control.

25. The method of claim 24, wherein the control is a kidney transplant under the standard of care of tacrolimus.

26. The method of claim 25, wherein the delaying of kidney transplant rejection is 10% or more relative to a kidney transplant under the standard of care of tacrolimus.

27. The method of claim 25 or 26, wherein the delaying of kidney transplant rejection is 20% or more relative to a kidney transplant under the standard of care of tacrolimus.

28. The method of any one of claims 25-27, wherein the delaying of kidney transplant rejection is 30% or more relative to a kidney transplant under the standard of care of tacrolimus.

29. The method of any one of claims 25-28, wherein the delaying of kidney transplant rejection is 40% or more relative to a kidney transplant under the standard of care of tacrolimus.

30. The method of any one of claims 25-29, wherein the delaying of kidney transplant rejection is 50% or more relative to a kidney transplant under the standard of care of tacrolimus.

31. A method of inhibiting kidney transplant rejection in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically binds CD40 ligand, wherein the inhibiting kidney transplant rejection is relative to a control.

32. The method of claim 31, wherein the control is a kidney transplant under the standard of care of tacrolimus.

33. The method of claim 32, wherein the inhibiting of kidney transplant rejection is 10% or more relative to a kidney transplant under the standard of care of tacrolimus.

34. The method of claim 32 or 33, wherein the inhibiting of kidney transplant rejection is 20% or more relative to a kidney transplant under the standard of care of tacrolimus.

35. The method of any one of claims 32-34, wherein the inhibiting of kidney transplant rejection is 30% or more relative to a kidney transplant under the standard of care of tacrolimus.

36. The method of any one of claims 32-35, wherein the inhibiting of kidney transplant rejection is 40% or more relative to a kidney transplant under the standard of care of tacrolimus.

37. The method of any one of claims 32-36, wherein the inhibiting of kidney transplant rejection is 50% or more relative to a kidney transplant under the standard of care of tacrolimus.

38. A method of restoring kidney function in a subject having a kidney transplant, wherein the method comprises administering to the subject in need thereof a therapeutically effective amount of an antibody or antigen binding fragment thereof that specifically

binds CD40 ligand, wherein the restored kidney function is measured by an aggregate mean estimated glomerular filtration rate (eGFR).

39. The method of claim 38, wherein kidney function is restored to an eGFR of greater than 50 mL/min/1.73 m^2.

40. The method of claim 38 or 39, wherein kidney function is restored to an eGFR of greater than 60 mL/min/1.73 m^2.

41. The method of any one of claims 38-40, wherein kidney function is restored to an eGFR of greater than 70 mL/min/1.73 m^2.

42. The method of any one of claims 38-41, wherein kidney function is restored to an eGFR of greater than 80 mL/min/1.73 m^2.

43. The method of any one of claims 38-42, wherein kidney function is restored to an eGFR of greater than 90 mL/min/1.73 m^2.

44. The method of claim 38, wherein kidney function is restored to a normal level following kidney transplant as measured by eGFR.

45. The method of any one of claims 1-44, wherein the subject is mammalian and/or human.

46. The method of any one of claims 1-45, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 100 mg/kg.

47. The method of any one of claims 1-46, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 50 mg/kg.

48. The method of any one of claims 1-47, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg to about 20 mg/kg.

49. The method of any one of claims 1-48, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 1 mg/kg, 5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg.

50. The method of any one of claims 1-49, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 20 mg/kg.

51. The method of any one of claims 1-49, wherein the therapeutically effective amount of the antibody or antigen binding fragment thereof is about 10 mg/kg.

52. The method of any one of claims 1-51, wherein the antibody or antigen binding fragment thereof is AT-1501.

53. The method of any one of claims 1-52, wherein the antibody or antigen binding fragment thereof comprises:

(a) a heavy chain variable region (VH) comprising:

i) a CDR1 domain comprising the sequence set forth in SEQ ID NO: 9;

ii) a CDR2 domain comprising the sequence set forth in SEQ ID NO: 74; and

iii) a CDR3 domain comprising the sequence set forth in SEQ ID NO. 15, and

(b) a light chain variable region (VL) comprising:

i) a CDR1 domain comprising the sequence set forth in SEQ ID NO: 72;

ii) a CDR2 domain comprising the sequence set forth in SEQ ID NO: 73; and

iii) a CDR3 domain comprising the sequence set forth in SEQ ID NO: 20.

54. The method of any one of claims 1-52, wherein the antibody or antigen binding fragment thereof comprises a light chain and a heavy chain, wherein the light chain comprises a light chain variable region comprising an amino acid sequence having at least 95% sequence identity with SEQ ID NO: 58, the heavy chain comprises a variable heavy chain region and an Fc region, wherein the heavy chain variable region comprises an amino acid sequence having at least 95% sequence identity with SEQ ID NO: 59, and the Fc region comprises the amino acid sequence set forth in SEQ ID NO: 60 or 61.

55. The method of any one of claims 1-52, wherein the antibody or antigen binding fragment thereof comprises a light chain and a heavy chain, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 64 and the heavy chain comprises the amino acid sequence of SEQ ID NO: 66.

56. The method of claim 55, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 66 and an Fc region comprising the amino acid sequence of SEQ ID NO: 60 or 61.

57. The method of any one of claims 1-56, wherein the antibody or antigen binding fragment thereof is administered at least once every three weeks.

58. The method of any one of claims 1-57, wherein the kidney transplant is a xenograft, allograft, or autograft.

59. The method of any one of claims 1-58, wherein the subject suffers from a disease or disorder.

60. The method of claim 59, wherein the disease or disorder is an autoimmune disease, wherein the autoimmune disease is systemic lupus erythematous, type-1 diabetes, myasthenia gravis, inflammatory bowel disease, immune thrombocytopenic purpura, rheumatoid arthritis, psoriasis, Addison's disease, Crohn's disease, uveitis, multiple sclerosis, hemolytic anemia, or Graves' disease.

61. The method of any one of claims 1-60, wherein the patient-to-donor HLA match is 4-6.

62. The method of any one of claims 1-61, wherein the kidney is from a donor less than 60 years of age.

63. The method of any one of claims 1-62, wherein the kidney is from a donor between 20-50 years of age.

64. The method of any one of claims 1-63, wherein the subject is less than 70 years of age.

65. The method of any one of claims 1-64, wherein the method further comprises administering one or more additional pharmaceutically effective compounds.

66. The method of claim 65, wherein the one or more additional compound blocks the interaction between CD28 and CD86 or between CD28 and CD80.

67. The method of claim 65, wherein the one or more additional compound targets at least one of the biomarkers selected from the group consisting of: interleukins, cytokines, and proinflammatory markers.

68. The method of claim 65, wherein the one or more additional compound is a CTLA4-Ig fusion protein, an abatacept, a belatacept, or a galiximab.

69. The method of any one of claims 1-68, wherein the one or more additional pharmaceutically effective compounds includes anti-thymocyte globulin, mycophenolate mofetil or mycophenolate sodium, or prednisone or a prednisone equivalent.

70. The method of any one of claims 1-68, wherein the one or more additional pharmaceutically effective compounds targets T-cells by one or more of clearing T-cells from circulation; or modulating T-cell activation, homing, or cytotoxic activities.

71. The method of claim 70, wherein the compound that targets T-cells is an anti-thymocyte globulin.

72. The method of any one of claims 1-71, wherein the one or more additional pharmaceutically effective compounds inhibits inosine monophosphate dehydrogenase.

73. The method of claim 71, wherein the compound that inhibits inosine monophosphate dehydrogenase is selected from a mycophenolate mofetil or a mycophenolate sodium.

74. The method of any one of claims 1-73, wherein the one or more additional pharmaceutically effective compounds is a corticosteroid.

75. The method of claim 74, wherein the corticosteroid is selected from methylprednisolone, prednisolone, prednisone, cortisone, hydrocortisone, betamethasone, dexamethasone, or triamcinolone.

76. The method of claim 74, wherein the corticosteroid is methylprednisolone or prednisolone.

77. The method of any one of claims 1-76, wherein the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered on days 1, 3, 7, 14, 21, and 28 and every 21 days thereafter after transplant.

78. The method of any one of claims 1-76, wherein the antibody or antigen binding fragment thereof that specifically binds CD40 ligand is administered on days 1, 7, 14, 21, and 28 and every 21 days thereafter after transplant.

79. The method of any one of claims 1-78, wherein the antibody or antigen binding fragment thereof is administered parenterally or intravenously.

80. The method of claim 79, wherein the antibody or antigen binding fragment thereof is administered by injection or infusion.

81. The method of claim 80, wherein the antibody or antigen binding fragment thereof is administered by intravenous, intramuscular, or subcutaneous injection.

82. The method of any one of claims 1-81, wherein the antibody or antigen binding fragment thereof is formulated in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.