

We Claim:

1. An isolated antibody that binds to CD154, comprising a ~~human or~~ humanized variable domain, wherein the variable domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), and wherein the VH is operably linked to a human Fc ~~domain with modified effector functions; region~~ derived from IgG4 and comprising S228P and L235A amino acid modifications; wherein the VH comprises

(a) a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 57,

(b) a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 58, and

(c) a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 59; and

wherein the VL comprises

(a) a light chain CDR1 having the amino acid sequence of SEQ ID NO: 60,

(b) a light chain CDR2 having the amino acid sequence of SEQ ID NO: 61, and

(c) a light chain CDR3 having the amino acid sequence of SEQ ID NO: 62.

2. ~~The antibody of claim 1, wherein one or more effector functions are reduced.~~

3. ~~The antibody of claim 1 or 2, wherein one or more effector functions are eliminated.~~

4. ~~The antibody of any one of claims 1-3, wherein the VH is operably linked to a human Fc region, wherein the human Fc region comprises a human hinge sequence and the human Fc domain, wherein the human hinge sequence is between the VH and the human Fc domain.~~

5. ~~The antibody of claim 4, wherein the hinge comprises the amino acid sequence of any one of SEQ ID NOs: 76-90.~~

6. ~~The antibody of any one of claims 1-5, wherein the Fc domain is derived from an IgG4 Fc (or crystallizable fragment) region.~~

7. ~~The antibody of claim 6, wherein the Fc domain comprises one or more amino acid modifications that modifies effector functions.~~

8. ~~The antibody of claim 7, wherein the antibody comprises an amino acid modification at any one of the positions selected from the group consisting of S228, L235, G237, E318, and N297 or a combination thereof, wherein the numbering of amino acid residues is according to the EU index as set forth in Edelman.~~

9. — The antibody of claim 8, wherein the antibody comprises an amino acid modification selected from the group consisting of S228P, F234A, L235A, L235E, G237A, E318A, and N297Q or a combination thereof.

10. — The antibody of any one of claims 1-5, wherein the Fc domain is derived from (or crystallizable fragment) region and comprises one or more amino acid modifications that modifies effector functions.

11. — The antibody of claim 10, wherein the antibody comprises an amino acid modification at any one of the positions selected from the group consisting of E216, R217, K218, C219, C220, C226, C229, P230, E233, L234, L235, G236, G237, P238, S239, V240, F241, K246, L251, T260, D265, V266, H268, W277, N297, E318, K322, P329, A330, P331, Q347, N348, T350, L351, K360, T366, N390, K392, T394, D399, S400, F405, Y407, K409, T411, or a combination thereof, wherein the numbering of amino acid residues is according to the EU index as set forth in Edelman.

12. — The antibody of claim 11, wherein the antibody comprises an amino acid modification selected from the group consisting of C220S, C226S, C229S, P230S, E233P, L234A, L234F, L234V, L235A, L235E, L235V, G236E, G237A, P238S, D265S, D265A, H268Q, W277T, N297G, N297Q, N297D, N297A, E318A, K322A, P329G, P329A, A330S, P331S, Q347R, Q347E, Q347K, T350V, L351Y, K360D, K360E, T366A, T366I, T366L, T366M, T366V, N390R, N390K, N390D, K392V, K392M, K392R, K392L, K392F, K392E, T394W, D399R, D399W, D399K, S400E, S400D, S400R, S400K, F405A, F405I, F405M, F405T, F405S, F405V, F405W, Y407A, Y407I, Y407L, Y407V, K409F, K409I, K409S, K409W, T411N, T411R, T411Q, T411K, T411D, T411E, T411W, ΔE216-E222, K246R/L251E/T260R, InR234/235, InV235/236, InR236/237, InR237/238, InV238/239, InN238/239, InL238/239, InE238/239, InG238/239, InS239/240, InG240/241, InE240/241, InG240/241, InL238/239/P238Q, InE238/239/N348A, InS239/240/V266A, and InR237/238/G236A or a combination thereof.

13. — The antibody of any one of claims 1-5, wherein the Fc domain is derived from an IgG2 Fc (or crystallizable fragment) crystallizable fragment region.

14. — The antibody of claim 13, wherein the antibody comprises an amino acid modification at any one of the positions selected from the group consisting of V234, G237, P238, H268, V309, A330, and P331 or a combination thereof, wherein the numbering of amino acid residues is according to the EU index as set forth in Edelman.

15. — The antibody of claim 14, wherein the antibody comprises an amino acid modification selected from the group consisting of V234A, G237A, P238S, H268Q, H268A, V309L, A330S, and P331S, or a combination thereof.

~~16. The antibody of any one of claims 1-5, wherein the Fc domain comprises the amino acid sequence selected from the group consisting of SEQ ID NOs: 3-9, 12-18, and 238-241.~~

~~17.2. The antibody according to claim 1~~claim 4~~, wherein the Fc region comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 23 or 42s; 21-37, 40-56, and 243-251.~~

~~18.3. The antibody of claim 1 or 2any one of claims 1-17, wherein the ~~VH~~ comprises~~

~~—— (a) a heavy chain comprises a constant region comprising the amino acid sequence of SEQ ID NO: 95 or 109CDR1 having the amino acid sequence of SEQ ID NO: 57,~~

~~—— (b) a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 58, and~~

~~—— (c) a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 59; and~~

~~wherein the VL comprises~~

~~—— (a) a light chain CDR1 having the amino acid sequence of SEQ ID NO: 60,~~

~~—— (b) a light chain CDR2 having the amino acid sequence of SEQ ID NO: 61, and~~

~~—— (c) a light chain CDR3 having the amino acid sequence of SEQ ID NO: 62.~~

~~19.4. The antibody of any one of claims 1-3~~claims 1-18~~, wherein the VH comprises the amino acid sequence selected from the group consisting of SEQ ID NO: 63, 64, 252 and 253.~~

~~20.5. The antibody of any one of claims 1-4~~claims 1-19~~, wherein the VL comprises the amino acid sequence of SEQ ID NO: 65 or 66.~~

~~21. The antibody of any one of claims 4-20, wherein the antibody further comprises a CH1 domain, wherein the CH1 domain is operably linked to~~

~~—— (a) the C-terminal end of the VH, and~~

~~—— (b) the N-terminal end of the hinge.~~

~~22. The antibody of claim 21, wherein the CH1 domain comprises an amino acid sequence that is at least 80% identical to the amino acid sequence of any one of SEQ ID NOs: 67, 70, and 73.~~

~~23. The antibody of any one of claims 1-22, wherein the antibody comprises a linker between the VH and the Fc domain.~~

~~24. The antibody of any one of claims 4-22, wherein the antibody comprises a linker between the VH and the hinge.~~

- ~~25. The antibody of claim 21 or 22, wherein the antibody comprises a linker between the VH and the CH1 domain.~~
- ~~26. The antibody of any one of claims 23-25, wherein the linker comprises the amino acid sequence of any one of SEQ ID NOs: 199-223 and 327-330.~~
- ~~27. The antibody of any one of claims 1-26, wherein the VH is operably linked to the amino acid sequence of any one of SEQ ID NOs: 3-9, 12-18, 21-37, 40-56, 238-241, and 243-251.~~
- ~~28. 6. The antibody of any one of claims 1-5~~claims 1-27~~, wherein the heavy chain comprises the amino acid sequence of any one of SEQ ID NO: 151 or 165~~s: 121-132, 135-146, 149, 151-160, 163, 165-174, 266-277, and 279-288.~~~~
- ~~29. 7. The antibody of any one of claims 1-6~~claims 1-28~~, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 195 or 196~~.~~~~
- ~~30. The antibody of any one of claims 1-29, wherein the antibody is monoclonal.~~
- ~~31. The antibody of any one of claims 1-30, wherein the antibody is chimeric.~~
- ~~32. The antibody of any one of claims 1-31, wherein the antibody is humanized.~~
- ~~33. The antibody of any one of claims 1-17, 21-27 and 30, wherein the antibody is human.~~
- ~~34. The antibody of any one of claims 1-33, wherein the binding of the antibody to human CD154 inhibits the interaction between human CD154 and human CD40.~~
- ~~35. The antibody of any one of claims 1-34, wherein the antibody blocks the activation of one or more of B cells, macrophages, dendritic cells, or endothelial cells by inhibiting binding of CD154 to CD40.~~
- ~~36. The antibody of any one of claims 1-35, wherein the antibody has one or more of the following effects when administered to a subject:~~
- ~~—— (a) decreased risk of thrombosis or thromboembolic events compared to hu5c8 antibody;~~
- ~~—— (b) decreased activation of platelets expressing CD154;~~
- ~~—— (c) inhibition of CD154 shedding; and~~
- ~~—— (d) alteration of the expression or activity of downstream targets of CD154-CD40 signaling.~~
- ~~37. The antibody of any one of claims 1-36, wherein the antibody has a K_D of less than 50 pM for CD154, such as 5-25 pM or 9.5-23 pM.~~

~~38. The antibody of any one of claims 1-37, wherein the antibody does not comprise the amino acid sequence consisting of any one of SEQ ID NOs: 119, 120, 133, 134, 147, 148, 150, 161, 162, 164, 230, 234 and 278.~~

8. An antibody comprising a light chain comprising the amino acid sequence of SEQ ID NO: 196 and a heavy chain comprising an amino acid sequence of SEQ ID NO: 151 or 165.

9.39. An isolated nucleic acid molecule encoding a light chain and a heavy chain of an anti-CD154 antibody of any one of claims 1-8~~claims 1-38.~~

~~40. An isolated nucleic acid molecule encoding an anti-CD154 antibody comprising the amino acid sequence of any one of SEQ ID NOs: 121-132, 135-146, 149, 151-160, 163, 165-174, 195, 196, 266-277, and 279-288.~~

~~41. A first isolated nucleic acid molecule and a second isolated nucleic acid molecule, wherein the first isolated nucleic acid molecule encodes a heavy chain comprising the amino acid sequence of any one of SEQ ID NOs: 121-132, 135-146, 149, 151-160, 163, 165-174, 266-277, and 279-288 and the second isolated nucleic acid molecule encodes a light chain comprising the amino acid sequence of SEQ ID NO: 195 or 196.~~

10.42. A first isolated nucleic acid molecule and a second isolated nucleic acid molecule, wherein the first isolated and second nucleic acid molecules encode, respectively, a heavy chain and a light chain of an anti-CD154 antibody of any one of claims 1-8~~claims 1-38.~~

11.43. A vector comprising the isolated nucleic acid molecule according to claim 9~~claim 39 or 40.~~

12.44. A first vector and a second vector, wherein the first vector comprises the first isolated nucleic acid molecule according to claim 10~~claim 41 or 42, and the second vector comprises the second isolated nucleic acid molecule according to claim 10~~~~claim 41 or 42.~~

13.45. A transformed cell comprising the isolated nucleic acid molecule according to claim 9~~claim 39 or 40, the first and second isolated nucleic acid molecules according to claim 10~~~~claim 41 or 42, the vector according to claim 11~~~~claim 43, or the first and second vectors according to claim 12~~~~claim 44.~~

14.46. A pharmaceutical composition comprising an anti-CD154 antibody of any one of claims 1-8~~claims 1-38 and a pharmaceutically acceptable carrier.~~

~~47. A pharmaceutical composition comprising the isolated nucleic acid molecule according to claim 39 or 40, the first and second isolated nucleic acid molecules according to claim 41 or 42, the vector according to claim 43, or the first and second vectors according to claim 44, and a pharmaceutically acceptable excipient.~~

~~48. A pharmaceutical composition comprising the transformed cell according to claim 45 and a pharmaceutically acceptable excipient.~~

15.49. A method of Use of the antibody of any one of claims 1-8 or the pharmaceutical composition of claim 14 in the preparation of a medicament for:

(a) inhibiting an immune response in a subject;

(b) treating or preventing a transplant rejection in the subject;

(c) inducing hematopoietic chimerism in a transplant recipient upon transplantation of hematopoietic stem cells into the recipient;

(d) inducing central tolerance in a transplant recipient upon transplantation of hematopoietic stem cells and a donor tissue into the recipient; or

(e) inhibiting xenotransplant rejection in a subject comprising administering to the subject a therapeutically effective amount of an antibody of any one of claims 1-38 or the pharmaceutical composition of claim any one of claims 46-48.

50.16. The method of claim 49 use of claim 15, wherein the immune response is a humoral response, an antibody-mediated response, or a cell-mediated response.

~~51. The method of claim 50, wherein the immune response is an antibody mediated response.~~

~~52. The method of claim 49, wherein the immune response is a cell mediated response.~~

~~53. The method of claim 52, wherein the cell mediated response is one or more of a cytotoxic T cell mediated immune response, a macrophage mediated response, a natural killer (NK) cell mediated immune response or a cytokine mediated response.~~

~~54. The method of claim 49, wherein the immune response is a mixed humoral and cell-mediated response.~~

~~55. The method of claim 54, wherein the mixed response is one or more of an antibody mediated response, a cytotoxic T cell mediated immune response, a macrophage mediated response, a natural killer (NK) cell mediated immune response or a cytokine mediated response.~~

~~56. The method of any one of claims 49-55, wherein the subject is human.~~

~~57. The method of any one of claims 49-55, wherein the subject is non human.~~

~~58. The method of claim 57, wherein the subject is a monkey.~~

~~17.59.~~ The use of claim 15 or 16~~method of any one of claims 49-58~~, wherein the subject has received or will receive a cell, tissue or organ transplant.

~~60.~~— The method of claim 59, wherein the transplant is an allogeneic transplant, autologous transplant or a xenogeneic transplant.

~~61.~~— The method of claim 59 or 60, wherein the cell is an engineered cell or an ex-vivo expanded cell.

~~62.~~— The method of claim 61, wherein one or more genes in the cell is modified using one or more techniques selected from a group consisting of transduction to express a cDNA, a CRISPR/Cas9 system, RNAi technology and retroviral technology.

~~63.~~— The method of claim 61 or 62, wherein the cell is modified to express a chimeric antigen receptor (CAR) on its surface.

~~64.~~— The method of any one of claims 59-63, wherein the cell is selected from a group consisting of a stem cell, a regulatory T cell, a CAR T cell, a CAR B cell, a tumor-infiltrating lymphocyte (TIL).

~~65.~~— The method of any one of claims 59-64, wherein the method comprises treating or preventing a transplant rejection in the subject.

~~66.~~— The method of claim 65, wherein the transplant rejection is an acute or a chronic humoral rejection

~~67.18.~~ The use of claim 15~~method of claim 65 or 66~~, wherein the transplant rejection is an acute or chronic graft rejection in a graft recipient of an allogeneic transplant or xenotransplant.

~~68.19.~~ The use of claim 18~~method of claim 66 or 67~~, wherein the ~~method~~ antibody or pharmaceutical compositions promotes a long-term graft survival of the grafted cell, tissue or organ, wherein said long-term graft survival is selected from the group consisting of:

- (a) at least 6 months post-transplant;
- (b) at least 1 year post-transplant; and
- (c) at least 5 years post-transplant.

~~69.20.~~ The use of any one of claims 15-19~~method of any one of claims 65-68~~, wherein the transplant rejection is associated with a hematopoietic cell or bone marrow transplant, an allogeneic transplant of pancreatic islet cells, graft vs host disease, or a solid organ transplant selected from the group consisting of a heart transplant, a kidney transplant, a liver transplant, a lung transplant, a pancreas transplant, a kidney-pancreas transplant, a heart-lung transplant, kidney-heart transplant, a kidney-heart-pancreas transplant, a heart-liver transplant, a heart-liver-kidney transplant, a heart-lung-kidney transplant, a heart-lung-liver transplant, a lung-kidney transplant, a lung-liver transplant, a liver-intestines-pancreas transplant, an

intestines-pancreas transplant, a liver-kidney-intestines-pancreas transplant, and a kidney-intestines transplant.

~~70.21. The method of any one of claims 56-58 use according to claim 15, wherein the subject has an immune-related disease, atherosclerotic disorder, or neurodegenerative disorder.~~

~~71. The method of any one of claims 56-58 and 70, wherein the subject had or is at risk of having a stroke, a transient ischemic attack (TIA), an aneurysm, or a dissecting aneurysm.~~

~~72.22. The method of claim 70 use according to claim 21, wherein:~~

~~(a) the immune-related disease is selected from a group consisting of type I diabetes, juvenile diabetes, autoimmune diabetes, autoimmune hemolytic anemia, rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriasis, multiple sclerosis, inflammatory bowel disease, Addison's disease, Crohn's disease, Graves' disease, Sjögren's syndrome, Hashimoto's thyroiditis, myasthenia gravis, vasculitis, pernicious anemia, celiac diseases, Guillain-Barre syndrome, ankylosing spondylitis, primary biliary cirrhosis, lupus nephritis, Goodpasture's disease, polymyositis, dermatomyositis, psoriasis, temporal arteritis, Churg-Strauss syndrome, transverse myelitis, thyroiditis, ulcerative colitis, sarcoidosis, hemolytic anemia, idiopathic thrombocytopenic purpura, neuromyelitis optica spectrum disorder, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, Behcet's disease, diabetic retinopathy (DR), diabetic macular edema (DME), wet age-related macular degeneration (AMD), severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), coronavirus disease 2019 (COVID-19), cytokine release syndrome (CRS), cytokine storm syndrome, acute respiratory distress syndrome (ARDS), pneumonia, bronchitis, pneumonitis, chronic obstructive pulmonary disease (COPD) and macular edema following retinal vein occlusion (MEfRVO);~~

~~(b) the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, traumatic brain injury (TBI), chronic traumatic encephalitis (CTE), amyotrophic lateral sclerosis (ALS) and Parkinson's disease; or~~

~~(c) the atherosclerotic disorder is selected from a group consisting of angina pectoris, myocardial infarction, carotid stenosis, transient ischemic attacks and cerebral vascular accident (CVA).~~

~~73. The method of claim 70, wherein the immune-related disease is selected from a group consisting of severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), coronavirus disease 2019 (COVID-19), cytokine release syndrome (CRS), and cytokine storm syndrome.~~

~~74. The method of claim 70, wherein the immune-related disease is selected from a group consisting of acute respiratory distress syndrome (ARDS), pneumonia, bronchitis, pneumonitis, and chronic obstructive pulmonary disease (COPD).~~

~~75. The method of claim 70, wherein the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, traumatic brain injury (TBI), chronic traumatic encephalitis (CTE), amyotrophic lateral sclerosis (ALS) and Parkinson's disease.~~

~~76. The method of claim 70, wherein the atherosclerotic disorder is selected from a group consisting of angina pectoris, myocardial infarction, carotid stenosis, transient ischemic attacks and cerebral vascular accident (CVA).~~

~~77. The method according to claim 70, wherein the immune-related disease is an allergic condition.~~

~~78. The method according to claim 77, wherein the allergic condition is selected from the group consisting of allergic rhinitis, asthma, atopic eczema, anaphylaxis, insect venom allergy, drug allergy, and food allergy.~~

~~79. The method of claim 49, wherein the immune response is a primary response or a secondary response.~~

~~80.23. The method of any one of claims 49-79 use according to any one of claims 15-22, wherein the antibody is formulated to be administered systemically, such as subcutaneously, intravenously, orally, via inhalation, transdermally, or rectally.~~

~~81. The method of claim 80, wherein the anti-CD154 antibody is administered subcutaneously, intravenously, intravitreally, orally, via inhalation, transdermally, or rectally.~~

~~82. The method of any one of claims 49-79, wherein the antibody is administered locally.~~

~~83. The method of any one of claims 49-82, wherein the anti-CD154 antibody is administered in combination with one or more additional agents selected from the group consisting of anti-thrombotic drugs, anti-platelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-allergy drugs.~~

~~84. The method of claim 83, wherein the anti-CD154 antibody is administered prior to, subsequently to, or simultaneously with the one or more additional agents.~~

~~85. The method of claim 83 or 84, wherein the anti-thrombotic drug is selected from a group consisting of a glycoprotein IIb/IIIa receptor antagonist, a direct or indirect factor Xa inhibitor and an anticoagulant.~~

~~86. The method of claim 85, wherein the anticoagulant is selected from a group consisting of heparin, warfarin, rivaroxaban, ximelgatan, dabigatran, apixaban, edoxaban, enoxaparin, and fondaparinux.~~

87. — The method of claim 85, wherein the glycoprotein IIb/IIIa receptor antagonist is selected from a group consisting of abciximab, rivaroxaban, apixaban, edoxaban, idrabiotaparinux, tirofiban, and eptifibatide.

88. — The method of claim 85, wherein the direct or indirect factor Xa inhibitor is selected from a group consisting of apixaban, idrabiotaparinux, fondaparinux, and rivaroxaban.

89. — The method of claim 83 or 84, wherein the anti-platelet drug is selected from the group consisting of drugs inhibiting the TXA₂ pathway, adenosine diphosphate (ADP) pathway inhibitors, thrombin inhibitors, Protease activated receptor 1 (PAR-1) inhibitors and phosphodiesterase (PDE) inhibitors.

90. — The method of claim 89, wherein the ADP pathway inhibitor is selected from a group consisting of clopidogrel, ticlopidine, prasugrel, ticagrelor, cangrelor and elinogrel.

91. — The method of claim 89, wherein the PDE inhibitor is selected from a group consisting of dipyridamole and cilostazol.

92. — The method of claim 83 or 84, wherein the NSAID is selected from the group consisting of acetylsalicylic acid (aspirin), celecoxib, diclofenac, diflunisal, etodolac, ibuprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tolmetin and prasugrel.

93. — The method of any one of claims 49-92, wherein the anti-CD154 antibody is administered in combination with one or more supplemental agents selected from the group consisting of immunosuppressive drugs, immunomodulatory drugs, anti-CD2 antibodies, anti-CD3 antibodies, anti-CD4 antibodies, anti-CD28 antibodies, anti-CD52 antibodies, mTOR inhibitors, calcineurin inhibitors, and antiviral drugs.

94. — The method of claim 93, wherein the anti-CD154 antibody is administered prior to, subsequently to, or simultaneously with the one or more supplemental agents.

95. — The method of claim 93 or 94, wherein the immunosuppressive drug or immunomodulatory drug is selected from the group consisting of cyclosporine A, tacrolimus (FK-506), doxorubicin, azathioprine, busulfan, cyclophosphamide, fludarabine, 5-fluorouracil, methotrexate, mycophenolate mofetil, mizoribine, leflunomide, a nonsteroidal anti-inflammatory, adrenocortical steroids, rapamycin, deoxyspergualin, FTY720, muromonab-CD3, alemtuzumab, basiliximab, daclizumab, eculizumab, rituximab, bortezomib, sipilizumab, anti-thymocyte globulin, leronlimab, siltuximab, sarilumab, tocilizumab, bevacizumab, ranibizumab, aflibercept and inhibitors of Bruton's tyrosine kinase (BTK), including zanubrutinib, acalabrutinib and ibrutinib and aflibercept.

96. — The method of claim 93 or 94, wherein the mTOR inhibitor is selected from the group consisting of rapamycin, everolimus, temsirolimus, ridaforolimus, and deforolimus.

97. — The method of claim 93 or 94, wherein the calcineurin inhibitor is selected from the group consisting of cyclosporine, tacrolimus (FK506), and pimecrolimus.

98. — The method of claim 93 or 94, wherein the antiviral drug is selected from the group consisting of ribavirin, interferon (alfacon-1), chloroquine, hydroxychloroquine, EIDD-2801, EIDD-1931, GS-5734, ivermectin, favipiravir, indomethacin, chlorpromazine, penciclovir, nafamostat, nitazoxanide, GS-44-524 and remdesivir.

99. — A method of inducing hematopoietic chimerism in a transplant recipient, the method consisting of administering to the recipient one or more doses of an anti-CD154 antibody, and transplanting into the recipient hematopoietic stem cells, thereby inducing hematopoietic chimerism in the recipient,

— wherein the anti-CD154 antibody is an anti-CD154 antibody according to any one of claims 1-38.

100.24. The method of claim 99 use of claim 15, wherein during the induction of hematopoietic chimerism the anti-CD154 antibody is formulated to be administered prior to, subsequently to or simultaneously with the transplantation of the hematopoietic stem cells.

101. The method of claim 99 or 100, wherein the anti-CD154 antibody is administered at a dose of 5-50 mg/kg.

102. The method of any one of claims 99-101, wherein the anti-CD154 antibody is administered subcutaneously, intravenously, intravitreally, orally, via inhalation, transdermally, or rectally.

103. The method of any one of claims 99-102, wherein the method further comprises a step of conditioning the transplant recipient prior to the transplantation with stem cells.

104. The method of claim 103, wherein the anti-CD154 antibody is administered prior to, subsequent to, or simultaneously with the conditioning step.

105. The method of claim 103 or 104, wherein the conditioning step is selected from a group consisting of total body irradiation, administration of one or more BCL-2 inhibitors, administration of busulfan, administration of fludarabine phosphate, administration of cyclophosphamide, administration of immunosuppressive one or more T cell-depleting antibodies, administration of cyclosporine A (CsA), administration of tacrolimus (FK-506), administration of one or more interleukin-2 (IL-2) receptor inhibitors, administration of IL-15 receptor inhibitors, administration of rapamycin, administration of one or more anti- $\alpha\beta$ T cell receptor antibodies, and administration of one or more CD122 antagonists,

~~administration of kidney donor derived CD34⁺ hematopoietic stem cells and CD3⁺ T cells (MDR-101 cellular therapy) or a combination thereof.~~

~~106. — The method of claim 105, wherein the one or more T cell-depleting antibodies are selected from the group consisting of anti-CD4, anti-CD8, anti-CD45, anti-CTLA4, anti-CD20, and anti-CD33 antibodies or a combination thereof.~~

~~107. — The method of claim any one of claims 99-106, wherein the transplant recipient has cancer.~~

~~108. — The method of claim any one of claims 99-107, wherein the transplant is a bone marrow transplant.~~

~~109. — A method of inducing central tolerance in a transplant recipient, the method comprising administering to the recipient one or more doses of an anti-CD154 antibody, transplanting into the recipient hematopoietic stem cells, and transplanting a donor tissue into the recipient, wherein the hematopoietic stem cells produce immune cells that are tolerant of the donor tissue, thereby inducing central tolerance in the recipient, and~~

~~— wherein the anti-CD154 antibody is an anti-CD154 antibody according to any one of claims 1-38.~~

~~110. — The method of claim 109, wherein the anti-CD154 antibody is administered prior to, subsequently to or simultaneously with the transplantation of the hematopoietic stem cells.~~

~~111. The method of claim 109 or 110, wherein the anti-CD154 antibody is administered at a dose of 5-50 mg/kg.~~

~~112. The method of any one of claims 109-111, wherein the anti-CD154 antibody is administered subcutaneously, intravenously, intravitreally, orally, via inhalation, transdermally, or rectally.~~

~~113. — The method of any one of claims 109-112, wherein the method further comprises one or more treatments to condition the recipient for hematopoietic stem cell transplantation.~~

~~114. — The method of claim 113, wherein the one or more treatments to condition the recipient for hematopoietic stem cell transplantation is selected from a group consisting of total body irradiation, administration of abatacept, administration of one or more BCL-2 inhibitors, administration of busulfan, administration of fludarabine phosphate, administration of cyclophosphamide, administration of one or more immunosuppressive T cell depleting antibodies, administration of cyclosporine A (CsA), administration of FK-506, administration of one or more interleukin-2 (IL-2) inhibitors, administration of rapamycin, administration of one or more anti- $\alpha\beta$ T cell receptor antibodies, and administration of one or more CD122 antagonists or a combination thereof.~~

~~115. The method of claim 114, wherein the one or more T cell-depleting antibodies are selected from the group consisting of anti-CD4, anti-CD8, anti-CD45, anti-CTLA4, anti-CD20, and anti-CD33 antibodies or a combination thereof.~~

~~116. A method of inhibiting xenotransplant rejection in a subject, comprising administering to the subject an effective amount of an anti-CD154 antibody, wherein the anti-CD154 antibody is an anti-CD154 antibody according to any one of claims 1-38.~~

~~117. The method of claim 116, wherein the anti-CD154 antibody is administered at a dose of 5-50 mg/kg.~~

~~118.25. The method of claim 116 or 117 use according to claim 15, wherein the xenotransplant is from a non-human donor selected from a group consisting of a pig, a mini-swine, and a non-human primate.~~

~~119. The method of claim 118, wherein the non-human donor is a pig or mini-swine that has been engineered to decrease or eliminate expression of one or more genes selected from the group consisting of porcine endogenous retroviruses (PERV), α -1,3-galactosyltransferase (GGTA1), cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH), β 1,4-N-acetylgalactosaminyltransferase (β 4GalNT2), and MHC class I.~~

~~120. The method of claim 119, wherein the PERV is a PERV A, a PERV B, or a PERV C.~~

~~121. The method of claim 119 or 120, wherein the expression of all PERV genes has been eliminated in the pig or mini-swine.~~

~~122. The method of any one of claims 119-121, wherein the expression of the one or more genes is decreased or eliminated using CRISPR/Cas9 gene editing.~~

~~123. The method of any one of claims 118-122, wherein the non-human donor has been engineered to express one or more human proteins selected from the group consisting of a complement regulatory protein, human α -galactosidase, a coagulation regulatory protein, a human anti-inflammatory protein, and human CTLA-4 Ig or a combination thereof.~~

~~124. The method of claim 123, wherein the one or more human proteins are expressed in all tissues of the non-human donor.~~

~~125. The method of claim 123, wherein the one or more human proteins are expressed in a tissue-specific manner in the non-human donor.~~

~~126. The method of any one of claims 123-125, wherein the complement regulatory protein is selected from the group consisting of human decay-accelerating factor (CD55), membrane cofactor protein (CD46) and CD59.~~

~~127. The method of any one of claims 123-125, wherein the coagulation regulatory proteins are selected from the group consisting of thrombomodulin, endothelial protein C receptor, tissue factor pathway inhibitor, CD39, and CD73.~~

~~128. The method of any one of claims 123-125, wherein the human anti-inflammatory proteins are selected from the group consisting of hemeoxygenase-1 (HO-1) and A20.~~

26,129. The method of any one of claims 116-128 use according to claim 15 or 25, wherein the xenotransplant rejection is associated with a solid organ transplant selected from the group consisting of a heart transplant, a kidney transplant, a liver transplant, a lung transplant, a pancreas transplant, a kidney-pancreas transplant, a heart-lung transplant, kidney-heart transplant, a kidney-heart-pancreas transplant, a heart-liver transplant, a heart-liver-kidney transplant, a heart-lung-kidney transplant, a heart-lung-liver transplant, a lung-kidney transplant, a lung-liver transplant, a liver-intestines-pancreas transplant, an intestines-pancreas transplant, a liver-kidney-intestines-pancreas transplant, and a kidney-intestines transplant.

~~130. The method of claim 49, wherein the immune response is complement-mediated.~~

~~131. The method of any one of claims 49-98, wherein the anti-CD154 antibody is administered in combination with one or more fusion peptides that bind to and block the function of CD28, optionally selected from the group consisting of abatacept and belatacept.~~

27. The antibody of any one of claims 1-8 or the pharmaceutical composition of claim 14 for use in:

(a) inhibiting an immune response in a subject;

(b) treating or preventing a transplant rejection in the subject;

(c) inducing hematopoietic chimerism in a transplant recipient upon transplantation of hematopoietic stem cells into the recipient;

(d) inducing central tolerance in a transplant recipient upon transplantation of hematopoietic stem cells and a donor tissue into the recipient; or

(e) inhibiting xenotransplant rejection in a subject.

28. The antibody or pharmaceutical composition of claim 27, wherein the immune response is a humoral response, an antibody-mediated response, or a cell-mediated response.

29. The antibody or pharmaceutical composition of claim 27 or 28, wherein the subject has received or will receive a cell, tissue or organ transplant.

30. The antibody or pharmaceutical composition of claim 27, wherein the transplant rejection is an acute or chronic graft rejection in a graft recipient of an allogeneic transplant or xenotransplant.

31. The antibody or pharmaceutical composition of claim 30, wherein the antibody or pharmaceutical composition promotes a long-term graft survival of the grafted cell, tissue or organ, wherein said long-term graft survival is selected from the group consisting of:

_____ (a) at least 6 months post-transplant;

_____ (b) at least 1 year post-transplant; and

_____ (c) at least 5 years post-transplant.

32. The antibody or pharmaceutical composition of any one of claims 27-31, wherein the transplant rejection is associated with a hematopoietic cell or bone marrow transplant, an allogeneic transplant of pancreatic islet cells, graft vs host disease, or a solid organ transplant selected from the group consisting of a heart transplant, a kidney transplant, a liver transplant, a lung transplant, a pancreas transplant, a kidney-pancreas transplant, a heart-lung transplant, kidney-heart transplant, a kidney-heart-pancreas transplant, a heart-liver transplant, a heart-liver-kidney transplant, a heart-lung-kidney transplant, a heart-lung-liver transplant, a lung-kidney transplant, a lung-liver transplant, a liver-intestines-pancreas transplant, an intestines-pancreas transplant, a liver-kidney-intestines-pancreas transplant, and a kidney-intestines transplant.

33. The antibody or pharmaceutical composition of claim 27, wherein the subject has an immune-related disease, atherosclerotic disorder, or neurodegenerative disorder.

34. The antibody or pharmaceutical composition of claim 27, wherein:

(a) the immune-related disease is selected from a group consisting of type I diabetes, juvenile diabetes, autoimmune diabetes, autoimmune hemolytic anemia, rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriasis, multiple sclerosis, inflammatory bowel disease, Addison's disease, Crohn's disease, Graves' disease, Sjögren's syndrome, Hashimoto's thyroiditis, myasthenia gravis, vasculitis, pernicious anemia, celiac diseases, Guillain-Barre syndrome, ankylosing spondylitis, primary biliary cirrhosis, lupus nephritis, Goodpasture's disease, polymyositis, dermatomyositis, psoriasis, temporal arteritis, Churg-Strauss syndrome, transverse myelitis, thyroiditis, ulcerative colitis, sarcoidosis, hemolytic anemia, idiopathic thrombocytopenic purpura, neuromyelitis optica spectrum disorder, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, Behcet's disease, diabetic retinopathy (DR), diabetic macular edema (DME), wet age-related macular degeneration (AMD), severe

acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), coronavirus disease 2019 (COVID-19), cytokine release syndrome (CRS), cytokine storm syndrome, acute respiratory distress syndrome (ARDS), pneumonia, bronchitis, pneumonitis, chronic obstructive pulmonary disease (COPD) and macular edema following retinal vein occlusion (MEfRVO);

(b) the neurodegenerative disorder is selected from a group consisting of Alzheimer's disease, traumatic brain injury (TBI), chronic traumatic encephalitis (CTE), amyotrophic lateral sclerosis (ALS) and Parkinson's disease; or

(c) the atherosclerotic disorder is selected from a group consisting of angina pectoris, myocardial infarction, carotid stenosis, transient ischemic attacks and cerebral vascular accident (CVA).

35. The antibody or pharmaceutical composition of any one of claims 27-34, wherein the antibody is formulated to be administered systemically, such as subcutaneously, intravenously, orally, via inhalation, transdermally, or rectally .

36. The antibody or pharmaceutical composition of claim 27, wherein during the induction of hematopoietic chimerism the anti-CD154 antibody is formulated to be administered prior to, subsequently to or simultaneously with the transplantation of the hematopoietic stem cells.

37. The antibody or pharmaceutical composition of claim 27, wherein the xenotransplant is from a non-human donor selected from a group consisting of a pig, a mini-swine, and a non-human primate.

38. The antibody or pharmaceutical composition of claim 27 or 37, wherein the xenotransplant rejection is associated with a solid organ transplant selected from the group consisting of a heart transplant, a kidney transplant, a liver transplant, a lung transplant, a pancreas transplant, a kidney-pancreas transplant, a heart-lung transplant, kidney-heart transplant, a kidney-heart-pancreas transplant, a heart-liver transplant, a heart-liver-kidney transplant, a heart-lung-kidney transplant, a heart-lung-liver transplant, a lung-kidney transplant, a lung-liver transplant, a liver-intestines-pancreas transplant, an intestines-pancreas transplant, a liver-kidney-intestines-pancreas transplant, and a kidney-intestines transplant.