

We Claim:

1. An isolated antibody that binds to CD154, comprising a 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 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 according to claim 1, wherein the Fc region comprises the amino acid sequence of SEQ ID NO: 23 or 42.

3. The antibody of-claim 1 or 2, wherein the-heavy chain comprises a constant region comprising the amino acid sequence of SEQ ID NO: 95 or 109.

4. The antibody of any one of claims 1-3, wherein the VH comprises the amino acid sequence of SEQ ID NO: 64.

5. The antibody of any one of claims 1-4, wherein the VL comprises the amino acid sequence of SEQ ID NO: 66.

6. The antibody of any one of claims 1-5, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 151 or 165.

7. The antibody of any one of claims 1-6, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 196.

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. 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.

10. 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.
11. A vector comprising the isolated nucleic acid molecule according to claim 9.
12. A first vector and a second vector, wherein the first vector comprises the first isolated nucleic acid molecule according to claim 10, and the second vector comprises the second isolated nucleic acid molecule according to claim 10.
13. A transformed cell comprising the isolated nucleic acid molecule according to claim 9, the first and second isolated nucleic acid molecules according to claim 10, the vector according to claim 11, or the first and second vectors according to claim 12.
14. A pharmaceutical composition comprising an anti-CD154 antibody of any one of claims 1-8 and a pharmaceutically acceptable carrier.
15. 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.
16. The use of claim 15, wherein the immune response is a humoral response, an antibody-mediated response, or a cell-mediated response.
17. The use of claim 15 or 16, wherein the subject has received or will receive a cell, tissue or organ transplant.
18. The use of claim 15, wherein the transplant rejection is an acute or chronic graft rejection in a graft recipient of an allogeneic transplant or xenotransplant.
19. The use of claim 18, 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.

20. The use of any one of claims 15-19, 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.

21. The use according to claim 15, wherein the subject has an immune-related disease, atherosclerotic disorder, or neurodegenerative disorder.

22. The 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).

23. The 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.

24. The 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.

25. The 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.

26. The 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.

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.