

CLAIMS

1. Use of an isolated anti-CD154 antibody in the preparation of a medicament for inducing immune tolerance in a transplant recipient who has received or will receive a transplant of hematopoietic stem cells and a transplant of a donor organ, a donor tissue or donor cell, wherein the hematopoietic stem cells produce immune cells that are tolerant of the donor organ, donor tissue or donor cell, thereby inducing immune tolerance in the recipient; wherein the isolated anti-CD154 antibody comprises 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 use of claim 1, wherein the tolerance is central tolerance.

3. The use of claim 2, wherein the T cells in the thymus and/or bone marrow of the recipient have been or will be depleted.

4. The use of claim 1, wherein the tolerance is (a) peripheral tolerance or (b) organ specific.

5. The use of claim 4, wherein (a) the T cells in the lymph nodes and/or peripheral tissue of the recipient have been or will be depleted or (b) the T cells from the heart, kidney, liver, lung, pancreas, intestines, islet cells, face, hand, arm, foot, leg or skin or a combination thereof of the recipient have been or will be depleted.

6. The use of any one of claims 3 and 5, wherein the T cells have been or will be depleted by a method 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 one or more anti- $\alpha\beta$ T cell receptor antibodies, and administration of one or more CD122 antagonists or a combination thereof.

7. The use of claim 6, 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.

8. The use of any one of claims 1-7, wherein the transplant recipient demonstrates mixed chimerism.

9. The use of any one of claims 1-8, wherein the anti-CD154 antibody is formulated to be administered prior to, subsequently to or simultaneously with the transplantation of the hematopoietic stem cells.

10. The use of any one of claims 1-9, wherein the anti-CD154 antibody is formulated to be administered at a dose of 5-50 mg/kg.

11. The use of any one of claims 1-10, wherein the anti-CD154 antibody is formulated to be administered subcutaneously, intravenously, intravitreally, orally, or rectally.

12. The use of claim 11, wherein the anti-CD154 antibody is formulated to be administered intravenously.

13. The use according to any one of claims 1-12, wherein the Fc region comprises the amino acid sequence of SEQ ID NO: 23 or 42.

14. The use of any one of claims 1-13, wherein the heavy chain comprises a constant region comprising the amino acid sequence of SEQ ID NO: 95 or 109.

15. The use of any one of claims 1-14, wherein the VH comprises the amino acid sequence-of SEQ ID NO: 64.

16. The use of any one of claims 1-15, wherein the VL comprises the amino acid sequence of SEQ ID NO: 66.

17. The use of any one of claims 1-16, wherein the heavy chain comprises the amino acid sequence of SEQ ID NO: 151 or 165.
18. The use of any one of claims 1-17, wherein the light chain comprises the amino acid sequence of SEQ ID NO: 196.
19. The use of any one of claims 1-18, wherein the anti-CD154 antibody comprises 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.
20. The use of any one of claims 1-19, wherein the transplant recipient is human.
21. The use of any one of claims 1-19, wherein the transplant recipient is a monkey.
22. The use of any one of claims 1-21, wherein the transplant is an allogeneic transplant, autologous transplant or a xenogeneic transplant.
23. The use of any one of claims 1-21, wherein the donor cell is an engineered cell or an ex-vivo expanded cell.
24. The use of claim 23, wherein one or more genes in the donor 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.
25. The use of claim 23 or 24, wherein the donor cell is modified to express a chimeric antigen receptor (CAR) on its surface.
26. The use of any one of claims 22-25, wherein the donor 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).
27. The use of any one of claims 1-26, wherein the anti-CD154 antibody is formulated to be administered locally.
28. The use of any one of claims 1-26, wherein the anti-CD154 antibody is formulated to be administered systemically.