CLAIMS

1. ~~A~~Use of an IL-2 agent in the manufacture of a medicament for ~~for use in a method of~~ treating or preventing a skin transplantation rejection in a subject,

wherein the IL-2 agent is ~~an IL-2 variant or~~ an IL-2 fusion protein comprising an ~~the~~ IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5~~:~~

~~(i) the amino acid substitution H16L or H16N, and/or the amino acid substitution I92S; and~~

~~(ii) the amino acid substitutions V69A, Q74P, and C125S,~~

~~corresponding to human IL-2 (SEQ ID NO: 1031)~~.

2. The ~~IL-2 agent for~~ use of claim 1, wherein the subject has received, is receiving, or will receive a skin transplantation.

~~3. An IL-2 agent for use in a method of treating a transplantation rejection in a subject,~~

~~wherein the IL-2 agent is an IL-2 variant or an IL-2 fusion protein comprising the IL-2 variant, and wherein the IL-2 variant comprises:~~

~~(i) the amino acid substitution H16L or H16N, and/or the amino acid substitution I92S; and~~

~~(ii) the amino acid substitutions V69A, Q74P, and C125S,~~

~~corresponding to human IL-2 (SEQ ID NO: 1031).~~

3~~4~~. The ~~IL-2 agent for~~ use of claim 1 ~~any one of claims 1-3~~, wherein the skin transplantation rejection is graft-vs-host disease (GVHD).

4~~5~~. ~~A~~Use of an IL-2 agent in the manufacture of a medicament for ~~use in a method of~~ conditioning a subject prior to a skin transplantation,

wherein the IL-2 agent is ~~an IL-2 variant or~~ an IL-2 fusion protein comprising an ~~the~~ IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5~~:~~

~~(i) the amino acid substitution H16L or H16N, and/or the amino acid substitution I92S; and~~

~~(ii) the amino acid substitutions V69A, Q74P, and C125S,~~

~~corresponding to human IL-2 (SEQ ID NO: 1031)~~.

5~~6~~. The ~~IL-2 agent for~~ use of claim 4~~5~~, wherein:

(i) conditioning a subject prior to the skin transplantation comprises increasing the number of T regulatory cells in the subject, or in a sample from the subject (*e.g.*, a peripheral blood sample);

(ii) conditioning a subject prior to the skin transplantation comprises increasing the ratio of T regulatory cells over non-T-regulatory T cells and/or NK cells in the subject or in a sample from the subject (e.g., a peripheral blood sample), optionally wherein the ratio is increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more; and/or

(iii) the IL-2 agent is used during the skin transplantation and/or after the skin transplantation.

~~7. The IL-2 agent for use of claim 5 or 6, wherein conditioning a subject prior to the transplantation comprises increasing the ratio of T regulatory cells over non-T-regulatory T cells in the subject or in a sample from the subject (*e.g.*, a peripheral blood sample), optionally wherein the ratio is increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more.~~

~~8. The IL-2 agent for use of any one of claims 5-7, wherein conditioning a subject prior to transplantation comprises increasing the ratio of T regulatory cells over NK cells in the subject, or in a sample (*e.g.*, a peripheral blood sample) from the subject, optionally wherein the ratio is increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more.~~

~~9. The IL-2 agent for use of any one of claims 5-8, wherein the method further comprises administering the IL-2 agent during the transplantation and/or after the transplantation.~~

6~~10~~. ~~A~~Use of an IL-2 agent in the manufacture of a medicament for ~~use in a method of~~ inducing and/or modulating (*e.g.*, increasing) immunosuppression in a subject,

wherein the subject has undergone, is undergoing, or will receive a skin transplantation,

wherein the IL-2 agent is an ~~IL-2 variant or an~~ IL-2 fusion protein comprising an ~~the~~ IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5~~:~~

~~(i) the amino acid substitution H16L or H16N, and/or the amino acid substitution I92S; and~~

~~(ii) the amino acid substitutions V69A, Q74P, and C125S,~~

~~corresponding to human IL-2 (SEQ ID NO: 1031)~~.

7~~11~~. The ~~IL-2 agent for~~ use of claim 6~~10~~, wherein:

(i) increasing immunosuppression in a subject comprises increasing the number of T-regulatory cells in the subject, or in a sample from the subject (*e.g.*, a peripheral blood sample); and/or

(ii) increasing immunosuppression in a subject prior to skin transplantation comprises increasing the ratio of T regulatory cells over non-T regulatory T cells and/or NK cells in the subject or in a sample from the subject (e.g., a peripheral blood sample), optionally wherein the ratio is increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more.

~~12. The IL-2 agent for use of claim 10 or 11, wherein increasing immunosuppression in a subject prior to transplantation comprises increasing the ratio of T regulatory cells over non-T regulatory T cells in the subject or in a sample from the subject (*e.g.*, a peripheral blood sample), optionally wherein the ratio is increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more.~~

~~13. The IL-2 agent for use of any one of claims 10-12, wherein increasing immunosuppression in a subject prior to transplantation comprises increasing the ratio of T regulatory cells over NK cells in the subject, or in a sample (*e.g.*, a peripheral blood sample) from the subject, optionally wherein the ratio is increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more.~~

8~~14~~. ~~A~~Use of an IL-2 agent in the manufacture of a medicament for ~~use in a method of~~ selectively increasing T regulatory cells in a subject,

wherein the subject has undergone, is undergoing, or will receive a skin transplantation, and

wherein the IL-2 agent is ~~an IL-2 variant or~~ an IL-2 fusion protein comprising an ~~the~~ IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5~~:~~

~~(i) the amino acid substitution H16L or H16N, and/or the amino acid substitution I92S; and~~

~~(ii) the amino acid substitutions V69A, Q74P, and C125S,~~

~~corresponding to human IL-2 (SEQ ID NO: 1031)~~.

9~~15~~. The ~~IL-2 agent for~~ use of claim 8~~14~~, wherein the T regulatory cells are increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more, relative to non-T regulatory T cells, NK cells, non-T regulatory CD4+ cells, and/or CD8+ cells.

~~16. The IL-2 agent for use of claim 14 or 15, wherein the T regulatory cells are increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more, relative to NK cells.~~

~~17. The IL-2 agent for use of any one of claims 14-16, wherein the T regulatory cells are increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more, relative to non-T regulatory CD4+ cells.~~

~~18. The IL-2 agent for use of any one of claims 14-17, wherein the T regulatory cells are increased by about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more, or about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more, relative to CD8+ cells.~~

10~~19~~. An IL-2 agent for use as a medicament in combination with a skin transplantation, wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5.

11~~20~~. Use of ~~The~~an IL-2 agent ~~for use of claim 19~~ in the manufacture of a medicament for:

(i) preventing a skin transplantation rejection in a subject;

(ii) inducing and/or modulating (e.g., increasing) immunosuppression in a subject; or

(iii) selectively increasing T regulatory cells in a subject,

wherein the IL-2 agent is an IL-2 fusion protein comprising an IL-2 variant, and wherein the IL-2 variant comprises the amino acid sequence of SEQ ID NO: 5, and wherein the medicament is to be used in combination with a skin transplantation.

12~~21~~. The ~~IL-2 agent for~~ use of claim 11~~20~~, wherein the skin transplantation rejection is graft versus host disease (GVHD).

~~22. The IL-2 agent for use of claim 19 in inducing and/or modulating (*e.g.*, increasing) immunosuppression in a subject.~~

~~23. The IL-2 agent for use of claim 19 in selectively increasing T regulatory cells in a subject.~~

1324. The ~~IL-2 agent for~~ use of claim 11 or 12~~any one of claims 20-23~~, wherein the IL-2 agent is to be administered to the subject prior to, during, and/or after the skin transplantation.

~~25. The IL-2 agent for use of any one of claims 1-24, wherein the transplantation is an organ transplant, a tissue transplant, or a cellular transplant.~~

~~26. The IL-2 agent for use of any one of claims 1-25, wherein the transplantation is a skin transplant.~~

1427. The ~~IL-2 agent for~~ use of any one of claims 1-9 or 11-13, or the IL-2 agent for use of claim 10~~20~~, ~~further comprising~~ wherein the medicament is to be used in combination with ~~administration of~~ one or more additional immunosuppressive agents chosen from cyclosporine, tacrolimus, mycophenolate mofetil, prednisone, azathioprine, sirolimus, daclizumab, or basiliximab.

~~28. The IL-2 agent for use of any one of claims 1-27, wherein the IL-2 agent is an IL-2 variant.~~

~~29. The IL-2 agent for use of any one of claims 1-27, wherein the IL-2 agent is an IL-2 fusion protein.~~

~~30. The IL-2 agent for use of any one of claims 1-29, wherein the IL-2 variant further comprises the amino acid substitution T3A.~~

~~31. The IL-2 agent for use of any one of claims 1-30, wherein the IL-2 variant comprises the amino acid sequence of any of SEQ ID NOs: 4, 5, 11, 1000, 1001, or 1002, an amino acid sequence that is at least 95% identical thereto or differs by no more than 1, 2, 3, 4, or 5 amino acids therefrom, or a functional fragment thereof.~~

1532. The use of any one of claims 1-9 or 11-14, or the IL-2 agent for use of claim 10 or 14 ~~IL-2 agent for use of any one of claims 1-27 or 29-31~~, wherein the IL-2 fusion protein further comprises an Fc region.

1633. The use of claim 15, or the IL-2 agent for use of claim 15 ~~IL-2 agent for use of claim 32~~, wherein the Fc region:

(i) comprises an Fc region of IgG1 allotype m3 comprising an N297G substitution according to EU numbering;

(ii) comprises the amino acid sequence of SEQ ID NO: 1003, or an amino acid sequence that is at least 95% identical thereto or differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids therefrom, or a functional fragment thereof; and/or

(iii) is fused to the C-terminus of the IL-2 variant.

~~34. The IL-2 agent for use of claim 32 or 33, wherein the Fc region comprises the amino acid sequence of SEQ ID NO: 1003, or an amino acid sequence that is at least 95% identical thereto or differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids therefrom, or a functional fragment thereof.~~

~~35. The IL-2 agent for use of any one of claims 32-34, wherein the Fc region is fused to the C-terminus of the IL-2 variant.~~

17~~36~~. The use of any one of claims 1-9 or 11-16, or the IL-2 agent for use of any one of claims 10 or 14-16~~IL-2 agent for use of any one of claims 1-27 or 29-35~~, wherein the IL-2 fusion protein further comprises a linker.

18~~37~~. The ~~IL-2 fusion protein for~~ use of claim 17 or the IL-2 agent for use of claim 17~~36~~, wherein the linker comprises the amino acid sequence $(G_4S)_4$ (SEQ ID NO: 48).

19~~38~~. The use of any one of claims 1-9 or 11-18, or the IL-2 agent for use of any one of claims 10 or 14-18 ~~IL-2 agent for use of any one of claims 1-27 or 29-37~~, wherein the IL-2 fusion protein comprises an amino acid sequence of ~~any of~~ SEQ ID NO~~s~~:~~1004, 1005, 1006, 1007,~~ 1008~~, or 1009~~, an amino acid sequence that is at least 95% identical thereto or differs by no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids therefrom, or a functional fragment thereof.

20. The use of any one of claims 1-9 or 11-19, or the IL-2 agent for use of any one of claims 10 or 14-19, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO: 1008.

21~~39~~. The use of any one of claims 1-9 or 11-20, or the IL-2 agent for use of any one of claims 10 or 14-20 ~~IL-2 agent for use of any one of claims 1-27 or 29-38~~, wherein the fusion protein forms a dimer.

2240. The use of any one of claims 1-9 or 11-21~~IL-2 agent for use of any one of claims 1-39~~, wherein the subject is a human, ~~or~~ a non-human primate, or a mouse.

~~41. The IL-2 agent for use of any one of claims 1-39, wherein the subject is a mouse.~~

2342. The use of any one of claims 1-9 or 11-22, or the IL-2 agent for use of any one of claims 10 or 14-22~~IL-2 agent for use of any one of claims 1-41~~, wherein the use further compris~~es~~ing determining the activity of T regulatory cells, *e.g.*, by an *ex vivo* suppression assay.