

CLAIMS

1. Use of a IL-2 fusion protein comprising an IL-2 variant and an Fc region in the manufacture of a medicament for treating a heart transplant rejection or a symptom thereof in a subject, wherein
5 IL-2 variant comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A, and Q74P.
2. Use of a IL-2 fusion protein comprising an IL-2 variant and an Fc region in the manufacture of a medicament for preventing a heart transplant rejection or the symptom thereof in a subject,
10 wherein IL-2 variant comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A, and Q74P.
3. Use of a IL-2 fusion protein comprising an IL-2 variant and an Fc region in the manufacture of a medicament for modulating (e.g., increasing or inducing) immunosuppression for a heart
15 transplant in a subject, wherein IL-2 variant comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A, and Q74P.
4. The use of any one of claims 1-3, wherein when the IL-2 fusion protein is to be administered to the subject, the subject has received, is to receive, or will receive a heart transplant.
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5. Use of a IL-2 fusion protein comprising an IL-2 variant and an Fc region in the manufacture of a medicament for conditioning the subject prior to a heart transplant, wherein IL-2 variant comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A, and Q74P.
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6. Use of a IL-2 fusion protein comprising an IL-2 variant and an Fc region in the manufacture of a medicament for selectively increasing Tregs in a subject, wherein the subject has received, is to receive, or will receive a heart transplant, wherein IL-2 variant comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A,
30 and Q74P.
7. Use of a IL-2 fusion protein comprising an IL-2 variant and an Fc region in the manufacture of a medicament for treating a heart disease or a symptom thereof in a subject in combination with a heart transplant, wherein IL-2 variant comprises an amino acid sequence having at least 95%
35 sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A, and Q74P.

8. The use of claim 7, wherein the heart transplant is provided to the subject prior to, concurrent with, or after administration of the IL-2 agent.

9. The use of any one of claims 1-8, wherein the level of Tregs in the subject is increased by about 2, 3, 4, 5, 6, 7, 8, 9, 10-fold or more, compared to the level of Tregs in the subject prior to administration of the IL-2 agent, optionally wherein the level of Tregs is determined in a sample from the subject.

10. The use of any one of the preceding claims, wherein the IL-2 variant further comprises the amino acid substitution T3A.

11. The use of any one of the preceding claims, wherein the IL-2 variant comprises (i) an amino acid sequence of any one of SEQ ID NOs: 4, 5, 11, 1000, 1001, or 1002, or (ii) an amino acid sequence that is at least 95% identical to any one of SEQ ID Nos: 4, 5, 11, 1000, 1001, or 1002.

12. The use of any one of the preceding claims, wherein the IL-2 variant comprises an amino acid sequence of SEQ ID NO: 5.

13. The use of any one of the preceding claims, wherein the Fc region comprises an Fc region of IgG1 allotype m3 comprising an N297G substitution according to EU numbering.

14. The use of any one of the preceding claims, 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 to SEQ ID NO: 1003.

15. The use of any one of the preceding claims, wherein the Fc region is fused to the C-terminus of the IL-2 variant.

16. The use of any one of the preceding claims, wherein the IL-2 fusion protein further comprises a linker, optionally wherein the linker comprises (G4S)₄ (SEQ ID NO: 48).

17. The use of any one of the preceding claims, wherein the fusion protein comprises an amino acid sequence of any one of SEQ ID NOs: 1004, 1005, 1006, 1007, 1008, or 1009; or (ii) an amino acid sequence that is at least 95% identical to any one of SEQ ID NOs: 1004, 1005, 1006, 1007, 1008, or 1009.

18. The use of any one of the preceding claims, wherein the fusion protein forms a dimer.

19. The use of any one of the preceding claims, further comprising the administration of an immunosuppressive agent to the subject.
- 5 20. The use of claim 19, wherein the immunosuppressive agent comprises rapamycin.
21. The use of any one of the preceding claims, wherein the subject is a human, a non-human primate, or a mouse.
22. A combination comprising an IL-2 fusion protein comprising an IL-2 variant and an Fc region, and a transplant, wherein IL-2 variant comprises an amino acid sequence having at least 95% sequence identity to SEQ ID NO: 1 and amino acid substitutions H16L, V69A, and Q74P.
23. The combination of claim 22, wherein the transplant is a heart transplant.
24. The combination of claim 22 or 23, further comprising one or more additional immunosuppressive agents, optionally wherein the immunosuppressive agent is rapamycin.
25. Use of the combination of any one of claim 22-24 in the manufacture of a medicament for treating or preventing a transplant rejection in a subject.
26. The use of claim 25, wherein the transplant rejection is a heart transplant rejection.
27. The use of claims 25 or 26, wherein the IL-2 fusion protein is to be administered to the subject prior to, during, and/or after the transplant.
28. Use of the combination of any one of claims 22-24 in the manufacturing of a medicament for modulating (e.g., increasing or inducing), immunosuppression in a subject or in selectively increasing T regulatory cells in a subject.
29. The use of any one of claims 25-28, wherein the subject is a human, a non-human primate, or a mouse.