

CLAIMS

1. An interleukin 2 (IL-2) mutein having:
 - (a) reduced binding affinity for interleukin 2 receptor γ (IL-2R γ) as compared to an IL-2 polypeptide encoded by SEQ ID NO: 2; and
 - (b) 15-95% $E_{\max}$ as compared to an IL-2 polypeptide encoded by SEQ ID NO: 2,wherein the mutein comprises
 - three or more amino acid substitutions selected from
 - (A) L18R and Q22E; and
 - (B) the amino acid position 126,
 - numbered in accordance with the amino acid sequence of SEQ ID NO: 2, the IL2 mutein optionally comprising the deletion of 1, 2, or 3 amino acids from the N-terminus,wherein the amino acid substitution at position 126 is selected from the group consisting of Q126A, Q126C, Q126D, Q126E, Q126G, Q126H, Q126I, Q126K, Q126M, Q126R, Q126S, and Q126T.
2. The IL-2 mutein of claim 1, wherein the mutein comprises the amino acid substitution Q126H, Q126K, or Q126M.
3. The IL-2 mutein of claim 1, wherein the mutein comprises an amino acid substitution Q126K.
4. The IL-2 mutein of any one of claims 1-3, wherein the mutein is structurally modified to increase half-life, wherein said modification to increase half-life comprises one or more modifications selected from the group consisting of fusion to a human Fc antibody fragment, fusion to albumin, and PEGylation.
5. The IL-2 mutein of any one of claims 1-4, wherein said mutein increases proliferation of regulatory T (T_{reg}).
6. The IL-2 mutein of any one of claims 1-5, wherein said mutein causes expansion of T_{reg} cells.
7. The IL-2 mutein of any one of claims 1-6, wherein the mutein has 70-95% $E_{\max}$ as compared to the polypeptide encoded by SEQ ID NO: 2.

8. A nucleic acid encoding the IL-2 mutein of any one of claims 1-7.
9. A vector comprising the nucleic acid of claim 8.
10. A host cell comprising the nucleic acid of claim 8 or the vector of claim 9.
11. A sterile pharmaceutical composition comprising the IL-2 mutein of any one of claims 1-7 and a pharmaceutically acceptable excipient.
12. A syringe comprising (a) the IL-2 mutein of any one of claims 1-19; (b) the nucleic acid of claim 8; (c) the vector of claim 9; (d) the host cell of claim 10; and/or (e) the pharmaceutical composition of claim 11.
13. A kit comprising:
 - (a) one or more of (i) the IL-2 mutein of any one of claims 1-7 or 23-28; (ii) the nucleic acid of claim 8; (iii) the vector of claim 9; (iv) the host cell of claim 10; (v) the sterile pharmaceutical composition of claim 11; and (vi) the syringe of claim 12 ; and
 - (b) written instructions for using the (i) the IL-2 mutein of any one of claims 1-7 or 23-28; (ii) the nucleic acid of claim 8; (iii) the vector of claim 9; (iv) the host cell of claim 10; (v) the sterile pharmaceutical composition of claim 11; and (vi) the syringe of claim 12.
14. Use of the (a) a therapeutically effective amount of the IL-2 mutein of any one of claims 1-7 or 23-28; (b) the nucleic acid of claim 8; (c) the vector of claim 9; (d) the host cell of claim 10; and/or (e) the pharmaceutical composition of claim 11 in the preparation of a medicament for the treatment of an autoimmune disease in an individual in need thereof.
15. The use of claim 14, wherein the autoimmune disease is selected from the group consisting of rheumatoid arthritis, insulin-dependent diabetes mellitus, hemolytic anemias, rheumatic fever, thyroiditis, Crohn's disease, myasthenia gravis, glomerulonephritis, autoimmune hepatitis, multiple sclerosis, alopecia areata, psoriasis, vitiligo, dystrophic epidermolysis bullosa, systemic lupus erythematosus, and graft vs. host disease.
16. The use of claim 14, wherein the autoimmune disease is graft vs. host disease.
17. The use of any one of claims 14-16, wherein the IL-2 mutein of any one of claims 1-7 or the pharmaceutical composition of claim 11 is to be administered in combination with an antibody that targets the mutein to a specific cell type.

18. The use of claim 17, wherein the cell type is a regulatory T (T_{reg}) cell.
19. The use of claim 17 or claim 18, wherein the antibody is covalently or non-covalently linked to the IL-2 mutein.
20. A method for producing the IL-2 mutein of any one of claims 1-7 comprising culturing the host cell of claim 10 under suitable conditions for the production of the mutein.
21. The method of claim 20 further comprising isolating and/or purifying the produced IL-2 mutein.
22. The method of claim 20 or 21, further comprising structurally modifying the IL-2 mutein to increase half-life,

wherein said modification comprises one or more alterations selected from the group consisting of fusion to a human Fc antibody fragment, fusion to albumin, and PEGylation.
23. The IL2 mutein of claim 5 wherein the IL2 mutein is PEGylated.
24. The IL2 mutein of claim 23 wherein PEGylation occurs at the N-terminus.
25. The IL2 mutein of claim 23 or 24 wherein the PEG has a molecular weight of approximately 10,000, 20,000, 30,000, or 40,000 daltons average molecular weight.
26. The IL2 mutein of any one of claims 23-25 wherein the PEG is a branched PEG.
27. The IL2 mutein of any one of claims 23-26 wherein the PEG has a molecular weight of 40,000 daltons average molecular weight.
28. The IL2 mutein of any one of claims 23-27 wherein the IL2 mutein comprises an N-terminal deletion of one amino acid residue (Ala1).