WHAT IS CLAIMED IS:

1. A variant human IL-2 protein comprising one or more amino acid changes, wherein the one or more amino acid changes is selected from the group consisting of:

(i) an amino acid substitution to methionine at position 27 (G27M~~),)~~;

(ii) an amino acid substitution at position 28~~,~~;

(iii) an amino acid substitution to alanine at position 31 (Y31A)~~,~~;

(iv) an amino acid substitution at position 32~~,~~ selected from the group consisting of a substitution to aspartic acid (K32D), a substitution to glutamic acid (K32E), and a substitution to serine (K32S);

(v) an amino acid substitution to serine at position 35 (K35S)~~,~~;

~~an amino acid substitution at position 39, an amino acid substitution at position 52,~~

(vi) an amino acid deletion at position 82 (P82Δ)~~,~~; and

(vii) an amino acid substitution to isoleucine at position 115 (V115I),

relative to the amino acid sequence of wild-type human IL-2 protein represented by SEQ ID NO: 19.

2. The variant human IL-2 protein of claim 1, wherein the variant human IL-2 protein comprises an amino acid substitution at position 28, relative to the amino acid sequence of wild-type IL-2 protein represented by SEQ ID NO: 19.

3. The variant human IL-2 protein of claim 2, further comprising an amino acid substitution at position 27, relative to the amino acid sequence of wild-type IL-2 protein represented by SEQ ID NO: 19.

4. The variant human IL-2 protein of claim 3, wherein the amino acid substitution at position 27 is a substitution to methionine (G27M).

5. The variant human IL-2 protein of any one of claims 2-4, further comprising an amino acid substitution at position 32, relative to the amino acid sequence of wild-type IL-2 protein represented by SEQ ID NO: 19.

~~2. A variant human IL-2 protein having greater potency for activation of IL-2 signaling pathways in cells lacking CD25 expression relative to wild type IL-2, comprising one or more amino acid substitutions relative to wild-type human IL-2.~~

~~3. The variant human IL-2 protein of claim 2, wherein the one or more amino acid substitutions relative to wild-type human IL-2 is selected from the group consisting of: an amino acid substitution to methionine at position 27 (G27M), an amino acid substitution at position 28, an amino acid substitution to alanine at position 31 (Y31A), an amino acid substitution at position 32, an amino acid substitution to serine at position 35 (K35S), an amino acid substitution at position 39, an amino acid substitution at position 52, and an amino acid substitution to isoleucine at position 115 (V115I).~~

~~4. The variant human IL-2 protein of claim 1 or 3 further comprising an amino acid deletion at position 81 (R81Δ) or a substitution at position 81.~~

~~5. The variant human IL-2 protein of claim 1 or 3 further comprising one or more amino acid substitutions at positions selected from the group consisting of: 69, 72, a region encompassing amino acid residues 74-80, 85, 86, and 92.~~

~~6. The variant human IL-2 protein of any one of claims 1 or 3-5, wherein the amino acid substitution at position 28 comprises a substitution to leucine (I28L).~~

~~7~~6. The variant human IL-2 protein of ~~any one of claims 1 or 3-6~~claim 5, wherein the amino acid substitution at position 32 is selected from the group consisting of: a substitution to aspartic acid (K32D), a substitution to glutamic acid (K32E), and a substitution to serine (K32S).

7. The variant human IL-2 protein of claim 5 or 6, wherein the amino acid substitution at position 32 is a substitution to aspartic acid (K32D).

8. The variant human IL-2 protein of any one of claims 2-7, wherein the amino acid substitution at position 28 comprises a substitution to leucine (I28L).

9. The variant human IL-2 protein of any one of claims 1-8, further comprising an amino acid substitution at position 72.

~~8. The variant human IL-2 protein of any one of claims 1 or 3-7, wherein the amino acid substitution at position 39 is selected from the group consisting of: a substitution to leucine (M39L) and a substitution to isoleucine (M39I).~~

~~9. The variant human IL-2 protein of any one of claims 1 or 3-8, wherein the amino acid substitution at position 52 is selected from the group consisting of: a substitution to serine (E52S), a substitution to aspartic acid (E52D), a substitution to asparagine (E52N), and a substitution to threonine (E52T).~~

~~10. The variant human IL-2 protein of any one of claims 5-9, wherein the amino acid substitution at position 69 comprises a substitution to alanine (V69A).~~

~~11~~10. The variant human IL-2 protein of ~~any one of claims 5-10~~claim 9, wherein the amino acid substitution at position 72 is selected from the group consisting of: a substitution to alanine (L72A), a substitution to glutamine (L72Q), a substitution to aspartic acid (L72D), a substitution to histidine (L72H), and a substitution to threonine (L72T).

11. The variant human IL-2 protein of claim 9 or 10, wherein the amino acid substitution at position 72 comprises a substitution to glutamine (L72Q).

12. The variant human IL-2 protein of any one of claims 1-11, further comprising an amino acid substitution at position 81.

~~12~~13. The variant human IL-2 protein of ~~any one of claims 4-11~~claim 12, wherein the amino acid substitution at position 81 comprises a substitution to aspartic acid (R81D).

14. The variant human IL-2 protein of any one of claims 8-13, wherein the amino acid changes comprise or consist of an amino acid substitution to methionine at position 27 (G27M), an amino acid substitution to leucine at position 28 (I28L), an amino acid substitution to aspartic acid at position 32 (K32D), an amino acid substitution to glutamine at position 72 (L72Q), and an amino acid substitution to aspartic acid at position 81 (R81D).

15. The variant human IL-2 protein of any one of claims 8-10, wherein the amino acid changes comprise or consist of an amino acid substitution to methionine at position 27 (G27M), an amino acid substitution to leucine at position 28 (I28L), an amino acid substitution to aspartic acid at position 32 (K32D), an amino acid substitution to leucine at position 39 (M39L), an amino acid substitution to serine at position 52 (E52S), an amino acid substitution to alanine at position 72 (L72A), a substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, an amino acid deletion at position 81 (R81Δ), an amino acid deletion at position 82 (P82Δ), an

amino acid substitution to valine at position 85 (L85V), an amino acid substitution to valine at position 86 (I86V), and an amino acid substitution to phenylalanine at position 92 (I92F).

~~13. The variant human IL-2 protein of any one of claims 5-12, wherein the amino acid substitution at position 85 is selected from the group consisting of: a substitution to valine (L85V), a substitution to methionine (L85M), and a substitution to alanine (L85A).~~

~~14. The variant human IL-2 protein of any one of claims 5-13, wherein the amino acid substitution at position 86 comprises a substitution to valine (I86V).~~

~~15. The variant human IL-2 protein of any one of claims 5-14, wherein the amino acid substitution at position 92 comprises a substitution to phenylalanine (I92F).~~

~~16. The variant human IL-2 protein of any one of claims 5-15, wherein the amino acid substitution at the region encompassing amino acid residues 74-80 comprises an amino acid sequence of GDDPKTI, DSTDETV, DSTDERI, DSTDSRI, SKDQDKV, SKDQKKV, SDDQDKV, ADDKDTI, or ADDQDKI.~~

~~17. The variant human IL-2 protein of claim 4 or 16 comprising amino acid changes G27M, I28L, K32D, M39L, E52S, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, and V115I.~~

~~18. The variant human IL-2 protein of claim 17 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72A, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, L85V, and V115I.~~

~~19. The variant human IL-2 protein of claim 17 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, V69A, L72A, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, and (V115I).~~

~~20. The variant human IL-2 protein of claim 17 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72A, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, and V115I.~~

~~21. The variant human IL-2 protein of claim 17 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72Q, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, and V115I.~~

~~22. The variant human IL-2 protein of claim 17 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72D, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, and V115I.~~

~~23. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32E, E52S, V69A, L72Q, substitution of the region encompassing amino acid residues 74-80 with GDDPKTI, R81Δ, P82Δ, and V115I.~~

~~24. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, V69A, L72Q, substitution of the region encompassing amino acid residues 74-80 with DSTDETV, R81Δ, P82Δ, and V115I.~~

~~25. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72A, substitution of the region encompassing amino acid residues 74-80 with DSTDERI, R81Δ, P82Δ, L85V, I86V, I92F, and V115I.~~

~~26. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72Q, substitution of the region encompassing amino acid residues 74-80 with DSTDSRI, R81Δ, P82Δ, and V115I.~~

~~27. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, substitution of the region encompassing amino acid residues 74-80 with SKDQKKV, R81Δ, P82Δ, L85V, I86V, I92F, and V115I.~~

~~28. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32S, M39L, E52S, V69A, substitution of the region encompassing amino acid residues 74-80 with SDDQDKV, R81Δ, P82Δ, L85V, I86V, I92F, and V115I.~~

~~29. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, V69A, L72H, substitution of the region encompassing amino acid residues 74-80 with ADDKDTI, R81Δ, P82Δ, and V115I.~~

~~30. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, Y31A, K32S, K35S, V69A, L72T, substitution of the region encompassing amino acid residues 74-80 with ADDQDKI, R81Δ, P82Δ, and V115I.~~

~~31. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, V69A, R81D, and V115I.~~

~~32. The variant human IL-2 protein of claim 31 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, V69A, L72Q, R81D, and V115I.~~

~~33. The variant human IL-2 protein of claim 4 or 16 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, R81D, and V115I.~~

~~34. The variant human IL-2 protein of claim 33 wherein the amino acid changes comprise or consist of G27M, I28L, K32D, M39L, E52S, V69A, L72Q, R81D, and V115I.~~

~~35. The variant human IL-2 protein of claim 4 wherein the amino acid changes consist of G27M, I28L, K32D, L72Q, and R81D.~~

16. The variant human IL-2 protein of any one of claims 1-15, wherein the variant human IL-2 protein has amino acid changes of no more than twenty amino acid residues relative to the amino acid sequence of wild-type human IL-2 protein represented by SEQ ID NO: 19.

~~36~~17. The variant human IL-2 protein of any one of claims 1-16, wherein the variant human IL-2 protein has a greater potency for activation of IL-2 signaling pathways in cells lacking CD25 expression relative to wild-type IL-2.

~~37~~18. The variant human IL-2 protein of any one of ~~the preceding~~ claims 1-17, wherein the variant human IL-2 protein has an EC_{50} for activation of IL-2 signaling pathways in cells lacking CD25 expression at least two-fold lower than the wild-type ~~protein~~IL-2.

~~38~~19. The variant human IL-2 protein of any one of ~~the preceding~~ claims 1-18, wherein the variant human IL-2 protein has increased binding affinity for human CD122, as measured in a surface plasmon resonance binding assay.

~~39~~20. The variant human IL-2 protein of any one of ~~the preceding~~ claims 1-19, wherein the variant human IL-2 protein has a greater potency for activation of IL-2 signaling pathways in cells lacking CD25 expression, but does not have a substantially increased binding affinity for CD122 relative to the wild type IL-2 protein.

~~40~~21. The variant human IL-2 protein of any one of ~~the preceding~~ claims 1-20, wherein the variant human IL-2 protein is fused to a human IgG Fc domain.

~~41~~22. The variant human IL-2 protein of claim ~~40~~21, wherein the human IgG Fc domain is an IgG1, IgG2, IgG3, or IgG4 Fc domain.

~~42~~23. A nucleic acid encoding a variant human IL-2 protein according to any one of ~~the preceding~~ claims 1-22.

~~43~~24. A vector comprising a nucleic acid encoding a variant human IL-2 protein according to claim 23~~according to claim 42~~.

~~44~~25. A recombinant cell comprising the nucleic acid according to claim ~~42~~ 23 or the vector according to claim ~~43~~24.

~~45~~26. A pharmaceutical composition comprising a variant human IL-2 protein ~~of~~ according to any one of claims 1-~~41~~22, and a pharmaceutically acceptable carrier.

~~46~~27. Use of the pharmaceutical composition of claim 26 in the manufacture of a medicament for~~A method of~~ treating a disease in a subject in need thereof~~, the method comprising administering to the patient a variant human IL-2 protein according to any one of claims 1-41, or the pharmaceutical composition of claim 45~~.

~~47~~28. Use of the pharmaceutical composition of claim 26 in the manufacture of a medicament for~~A method of~~ treating a disease in a subject in need of expansion of T cells~~, the method comprising administering an effective amount of a variant human IL-2 protein according to any of claims 1-41 or the pharmaceutical composition of claim 45~~.

~~48~~29. The ~~method~~ use of claim ~~46~~ 27 or ~~47~~28, wherein the disease is a hyperproliferative disease.

~~49~~30. The ~~method~~ use of ~~any one of claims 46-48~~claim 29, wherein the hyperproliferative disease is cancer.

31. The pharmaceutical composition of claim 26 for use in therapy.

~~50~~32. A method for in silico design of a cytokine based on crystallographic topology of the ligand receptor interaction, the method comprising: identifying locations where packing can be improved in order to increase binding; redesigning core positions and testing in a computer model to identify positions where improvements can be introduced: generating backbone structure ensembles while allowing the entire core to redesign while monitoring the residue changes in the identified regions; visually selecting a subset of resides that improve packing; holding identities of the subset and iteratively performing the redesign until the sequences converge; generating a coding sequence for the in silico designed cytokine.