

WHAT IS CLAIMED IS:

- 1 1. A fusion protein, comprising a human IL-2 variant protein domain, a
2 peptide linker segment domain of between 6 and 35 amino acids and an IgG Fc domain
3 where each domain has an amino-terminus (N-terminus) and a carboxy terminus (C-
4 terminus); and where the fusion protein is configured so that the C-terminus of the human IL-
5 2 variant protein domain is fused through a peptide bond to the N-terminus of the peptide
6 linker and the N-terminus of the IgG Fc protein moiety is fused through a peptide bond to the
7 C-terminus of the peptide linker;
8 wherein said IL-2 fusion protein has the ability to selectively activate the high
9 affinity IL-2 receptor and thus selectively activate human regulatory T cells.
- 1 2. The fusion protein of claim 1, wherein the IL-2 variant protein
2 comprises human IL-2 with a substitution selected from the group consisting of: N88R,
3 N88G, D20H, Q126L, and Q126F, relative to human IL2 protein (SEQ ID NO:1).
- 1 3. The fusion protein of claim 1, wherein the IL-2 variant protein
2 comprises human IL-2 with the substitution C125S.
- 1 4. The fusion protein of claim 1, wherein both the IL-2 variant protein is
2 N88R provided in SEQ ID NO:1.
- 1 5. The fusion protein of claim 1, where the linker comprises glycine and
2 serine residues and where the linker is between 10 and 30 amino acids.
- 1 6. The fusion protein of claim 1, wherein the IgG Fc protein contains one
2 or more amino acid substitutions that reduce the effector functions of the Fc portion of the
3 fusion protein.
- 1 7. A fusion protein, comprising:
2 a. a IL-2 variant protein having amino acid substitutions N88R and
3 C125S relative to human IL-2 (SEQ ID NO:1);
4 b. a linker peptide as set forth in SEQ ID NO:15; and,
5 c. a human IgG1 Fc variant protein as set forth in SEQ ID NO:2,
6 wherein said fusion protein has the ability to selectively activate the high
7 affinity IL-2 receptor and thus selectively activate human regulatory T cells.

- 1 8. A fusion protein, comprising
2 a. a IL-2 variant protein having amino acid substitutions N88R and
3 C125S relative to human IL-2 (SEQ ID NO:1);
4 b. a linker peptide as set forth in SEQ ID NO:15; and,
5 c. a human IgG2 Fc protein as set forth in SEQ ID NO:3.
- 1 9. A pharmaceutical composition comprising the fusion protein of claim
2 1 and a pharmaceutically acceptable carrier.
- 1 10. A method of selectively activating human regulatory T cells, the
2 method comprising administering a pharmaceutical composition comprising: a IL-2 variant
3 protein having amino acid substitutions N88R and C125S relative to human IL-2 (SEQ ID
4 NO:1), a linker peptide as set forth in SEQ ID NO:15, and a human IgG1 Fc protein as set
5 forth in SEQ ID NO:2, wherein said pharmaceutical composition is administered at
6 therapeutically effective dose until human regulatory T cell concentrations reach desired
7 levels.
- 1 11. A method of selectively activating human regulatory T cells, the
2 method comprising administering a pharmaceutical composition comprising: a IL-2 variant
3 protein of claim 2; and a human IgG Fc protein selected from group consisting of
4 a. a human IgG1 Fc protein as set forth in SEQ ID NO:2;
5 b. a human IgG2 Fc protein as set forth in SEQ ID NO:3; and,
6 c. a human IgG4 Fc protein domain as set forth in SEQ ID NO: 24
7 wherein said pharmaceutical composition is administered at therapeutically
8 effective dose until human regulatory T cell concentrations reach desired levels.
- 1 12. A method of measuring the numbers of Treg cells in a human blood
2 sample by contacting human blood cells with the fusion protein of claim 1 at a concentration
3 of between 1 nM and 0.01 nM, and then detecting cells that bind to the protein by flow
4 cytometry.
- 1 13. A dimeric protein, comprising two identical chains, where each chain
2 comprises a N-terminal human IL-2 variant protein moiety and a C-terminal IgG Fc protein
3 moiety wherein:
4 the N-terminal human IL-2 variant protein moiety

- 5 a. has a N-terminus and a C- terminus;
- 6 b. varies from the human IL-2 wildtype as in SEQ ID NO 1 by at least
7 one substitution selected from the group consisting of: N88R, N88G, D20H, Q126L, and
8 Q126F;
- 9 c. has at least a 97% sequence identify to Sequence ID No. 1; and,
- 10 d. has the ability activate Treg cells by binding to a IL2R $\alpha\beta\gamma$ on those
11 cells;
- 12 the N-terminal human IL-2 variant protein is joined at its C-terminal to a N-
13 terminus of an amino acid linker of between 6 to 30 amino acid residues where said linker
14 also has a C-terminus; and,
- 15 the C-terminus of the amino acid linker is joined to the N-terminus of IgG Fc
16 protein moiety having 95% sequence identify to sequence ID No. 2 and comprising cysteine
17 residues; and where the two chains are linked to each other through the cysteine residues of
18 the IgG Fc protein moiety.
- 1 14. The dimeric protein of claim 13, wherein the IL-2 variant protein
2 further comprises human IL-2 with the substitution C125S.
- 1 15. The protein of claim 13 wherein the amino acid linker consists of a
2 linker selected from the group of glycine residues, serine residues, and a mix of glycine and
3 serine residues.
- 1 16. The protein of claim 13, wherein the IL-2 variant protein moiety has
2 the substitution N88R.
- 1 17. The protein of claim 13 wherein the linker comprises a mix of
2 between 12 and 17 serine and glycine residues.
- 1 18. The fusion protein of claim 13 wherein the linker comprises a 4:1 ratio
2 of Glycine residues to serine residues.
- 1 19. A nucleic acid encoding the fusion protein of claim 1.