

T3A/D20N/N71K/C125S; T3A/D20N/R38I/C125S; T3A/D20N/T37R R38I/C125S;
T3A/D20N/R38I/N71K/C125S; T3A/D20N/C125S; T3A/D20N/T37R/C125S;
T3A/D20N/N71K/C125S; T3A/D20N/R38I/C125S; T3A/D20N/T37R/R38I/C125S;
T3A/D20N/R38I/N71K/C125S; and
N29S/Y31H/K35R/T37A/K48E/V69A/N71R/Q74P/N88D/I89V/C125S/Q126T.

[0008] In further examples, the disclosure provides IL-2-Fc fusion dimeric proteins comprising: a) a first monomer comprising, from N- to C-terminal: i) a variant IL-2 protein according to any of claims A1 to A4; ii) a first domain linker; and iii) a first variant Fc domain; and b) a second monomer comprising a second variant Fc domain.

[0009] In additional examples, the invention provides IL-2-Fc fusion dimeric proteins wherein said second monomer comprises, from N- to C-terminal: a) a variant IL-2 protein according to any of claims A1 to A4; b) a second domain linker; and c) said second variant Fc domain.

[0010] In further example is the IL-2-Fc fusion dimeric proteins have first and second variant Fc domains contain heterodimerization variants selected from the group consisting of L368D/K370S : S364K/E357Q; L368D/K370S : S364K; L368E/K370S : S364K;/T411E/K360E/Q362E : D401K; and T366S/L368A/Y407V : T366W. In some cases, the IL-2-Fc fusion proteins further comprise ablation variants, including P233P/L234V/L235A/G236_/S267K. In some examples the fusion proteins also comprise Fc domains with amino acid substitutions M428L/N434S or M428L/N434A. In some examples, the domain linker is the IGG1 hinge, and in others it can include a linker selected from (GS)_n, (GSGGS)_n, (GGGGS)_n, and (GGGS)_n, where n is an integer of at least one.

[0011] In one ~~aspect~~example, the present disclosure refers to a polypeptide composition comprising a variant human IL-2 protein wherein said variant IL-2 protein comprises amino acid substitution(s) as compared to SEQ ID NO:2 selected from the group of T3A/D20N/T37R and T3A/D20N/N71K. In some cases, the variant IL-2 protein further comprises a C125S variant or a C125A variant.

[0012] In a further example, the polypeptide composition is a homodimeric protein complex wherein each protein monomer comprises said variant IL-2 protein covalently attached to an Fc domain. In some examples, each of said Fc domains is a variant Fc domain.

[0018a] In one aspect, the present disclosure refers to an IL-2 fusion protein comprising: a) a first monomer having the sequence of SEQ ID NO: 297; b) a second monomer having the sequence of SEQ ID NO: 298. In yet another aspect, the present disclosure refers to an IL-2 fusion protein comprising: a) a first monomer having the sequence of SEQ ID NO: 295; b) a second monomer having the sequence of SEQ ID NO: 296. In another ~~aspect~~example, the present disclosure refers to a nucleic acid composition comprising a nucleic acid encoding the variant human IL-2 protein as disclosed herein.

[0018b] In another aspect, the present disclosure refers to a nucleic acid composition comprising: a) a first nucleic acid encoding said first ~~protein~~ monomer as disclosed herein; and b) a second nucleic acid encoding said second ~~protein~~ monomer as disclosed herein, respectively.

[0018c] In another aspect, the present disclosure refers to an expression vector composition comprising: a) a first expression vector comprising ~~said the~~ first nucleic acid as disclosed herein; and b) a second expression vector comprising ~~said the~~ second nucleic acid as disclosed herein.

[0018d] In another aspect, the present disclosure refers to a host cell comprising the expression vector composition as disclosed herein.

[0018e] In another aspect, the present disclosure refers to a method of making a an IL-2 Fc fusion protein~~polypeptide composition~~ comprising culturing the host cell as disclosed herein under conditions wherein the IL-2-Fc fusion protein~~said composition~~ is produced and recovering the IL-2-Fc fusion proteins~~said composition~~.

[0019] In a further example, the IL-2-Fc fusion dimeric protein is selected from XENP24635; XENP24636; XENP24637; XENP24638; XENP24639; XENP24640; XENP24641; XENP24642;

WHAT IS CLAIMED IS:

- ~~1. A polypeptide composition comprising a variant human IL-2 protein wherein said variant IL-2 protein comprises amino acid substitution(s) as compared to SEQ ID NO:2 selected from the group of T3A/D20N/T37R and T3A/D20N/N71K.~~
- ~~2. A polypeptide composition according to claim 1 wherein said variant IL-2 protein further comprises a C125S variant.~~
- ~~3. A polypeptide composition according to claim 1 wherein said IL-2 variant further comprises a C125A variant.~~
- ~~4. A polypeptide composition according to claim 1, 2 or 3 wherein said polypeptide composition is a homodimeric protein complex wherein each protein monomer comprises said variant IL-2 protein covalently attached to an Fc domain.~~
- ~~5. A polypeptide composition according to claim 4 wherein each of said Fc domains is a variant Fc domain.~~
- ~~6. A polypeptide composition according to claim 1, 2 or 3 wherein said polypeptide composition is a heterodimeric protein complex comprising a first protein monomer comprising said variant IL-2 protein is covalently attached to a first variant Fc domain and a second protein monomer comprising a second variant Fc domain.~~
- ~~7. A polypeptide composition according to claim 5 or 6 wherein said variant Fc domains are variant human IgG1 Fc domains comprising the amino acid substitutions M428L/N434S.~~
- ~~8. A polypeptide composition according to claim 5 or 6 wherein said variant Fc domains are variant human IgG1 Fc domains comprising the amino acid substitutions E233P/L234V/L235A/G236del/S267K.~~
- ~~9. A polypeptide composition according to claim 6, 7 or 8 wherein said first and second variant Fc domains comprise a set of heterodimerization variants selected from the group consisting of those depicted in Figure 2.~~
- ~~10. A polypeptide composition according to claim 9 wherein said set of heterodimerization variants selected from the group consisting of L368D/K370S; S364K/E357Q; L368D/K370S;~~

S364K; L368E/K370S : S364K; T411E/K360E/Q362E : D401K; and T366S/L368A/Y407V :
T366W.

~~11. A polypeptide composition according to claim 6, 7, 8, 9 or 10 wherein one of said variant Fe domains comprise a set of pI variants selected from the group consisting of those depicted in Figure 3.~~

~~12. A polypeptide composition according to claim 11 wherein said pI variant set is A295E/N384D/Q418/N421D.~~

~~13. A polypeptide composition according to 6 wherein said polypeptide composition is selected from the group consisting of XENP27564 (SEQ ID NOs:297 and 298), XENP27563 (SEQ ID NOs:295 and 296), XENP26105 (SEQ ID NOs:245 and 246), and XENP26109 (SEQ ID NOs:249 and 250).~~

1. An IL-2 fusion protein comprising:

_____ a) a first monomer having the sequence of SEQ ID NO: 297;

_____ b) a second monomer having the sequence of SEQ ID NO: 298.

~~14. A nucleic acid composition comprising a nucleic acid encoding the variant human IL-2 protein according to claim 1.~~

215. A nucleic acid composition comprising:

a) a first nucleic acid encoding said the first ~~protein~~ monomer of ~~any of claims 6 to claim 13~~; and

b) a second nucleic acid encoding said the second ~~protein~~ monomer of ~~any of claims 6 to claim 13~~, respectively.

316. An expression vector composition comprising:

a) a first expression vector comprising said the first nucleic acid of claim 215; and

_____ b) a second expression vector comprising said the second nucleic acid of claim 215.

417. A host cell comprising the expression vector composition according to claim 316.

518. A method of making ~~a polypeptide composition~~ an IL-2 Fc fusion protein -comprising culturing the host cell of claim ~~41~~ under conditions wherein ~~said composition~~ the IL-2-Fc fusion protein -is produced and recovering ~~said composition.~~ the IL-2-Fc fusion protein.

6. An IL-2 fusion protein comprising:

_____ a) a first monomer having the sequence of SEQ ID NO: 295;

_____ b) a second monomer having the sequence of SEQ ID NO: 296.

7. A nucleic acid composition comprising:

_____ a) a first nucleic acid encoding the first monomer of claim 6; and

_____ b) a second nucleic acid encoding the second monomer of claim 6, respectively.

8. An expression vector composition comprising:

_____ a) a first expression vector comprising the first nucleic acid of claim 7; and

_____ b) a second expression vector comprising the second nucleic acid of claim 7.

9. A host cell comprising the expression vector composition according to claim 8.

10. A method of making an IL-2 Fc fusion protein comprising culturing the host cell of claim 9 under conditions wherein the IL-2-Fc fusion protein is produced and recovering the IL-2-Fc fusion protein.