

CLAIMS

What is claimed is:

1. A composition comprising an IL-12 variant polypeptide, wherein said IL-12
5 variant polypeptide possesses sub-maximal signaling efficacy through its receptors relative to wild-type (WT) IL-12, wherein said IL-12 variant polypeptide comprises a p35 subunit (IL-12p35) with or without a signal peptide and a p40 subunit (IL-12p40) with or without a signal peptide and said IL-12p40 of said IL-12 variant polypeptide comprises at least one mutation selected from the group consisting of: H216X, K217X, and K219X,
10 relative to SEQ ID NO: 1, wherein X represents any amino acid.
2. The composition of claim 1, wherein said IL-12p40 of said IL-12 variant polypeptide comprise at least two mutations selected from the group consisting of: H216X, K217X, and K219X, relative to SEQ ID NO: 1, wherein X represents any amino
15 acid.
3. The composition of claim 2, wherein said IL-12p40 of said IL-12 variant polypeptide comprises H216X, K217X, and K219X mutations, relative to SEQ ID NO: 1, wherein X represents any amino acid.
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4. The composition of any one of claims 1 to 3, wherein said IL-12p40 of said IL-12 variant polypeptide comprises at least one mutation selected from the group consisting of: H216A, K217A, and K219A, relative to SEQ ID NO: 1.
- 25 5. The composition of any one of claims 1 to 4, wherein said IL-12p40 of said IL-12 variant polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.

6. The composition of claim 5, wherein said IL-12p40 of said IL-12 variant polypeptide comprises the amino acid sequence of SEQ ID NO: 9.
7. The composition of any one of claims 1 to 6, wherein said IL-12p35 of the IL-12 variant polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 30 and SEQ ID NO: 35.
8. The composition of any one of claims 1 to 7, further wherein at least one of said IL-12p40 and said IL-12p35 is fused to at least one *in vivo* half-life extending fusion selected from a group consisting of: an IgG Fc domain, an IgG Fc variant domain, human serum albumin (HSA), polyethylene glycol (PEG), and an anti-HSA nanobody.
9. The composition of claim 8, wherein at least one of said IL-12p40 and said IL-12p35 is fused to at least one said IgG Fc domain and said IgG Fc domain comprises a human IgG1 domain comprising an amino acid sequence of SEQ ID NO: 10, and wherein said IgG Fc variant domain comprises at least one selected from a group consisting of: a human IgG1 Fc “knob” domain comprising an amino acid sequence of SEQ ID NO: 14; and a human IgG1 Fc “hole” domain comprising an amino acid sequence of SEQ ID NO: 15.
10. The composition of claim 9, wherein said IL-12 variant polypeptide comprises a bivalent homodimeric IgG Fc comprising at least two human IgG1 Fc domains.
11. The composition of claim 9, wherein said IL-12 variant polypeptide comprises a bispecific heterodimeric IgG Fc comprising at least one human IgG1 Fc “knob” and at least one IgG Fc “hole”.
12. The composition of claim 9, wherein said IL-12 variant polypeptide comprises a single chain bivalent homodimeric IgG Fc comprising said IL-12p40 fused to said IL-12p35 via a linker and at least two human IgG1 Fc domains.

13. The composition of claim 9, wherein said IL-12 variant polypeptide comprises a single chain monomeric IL-12 comprising IL-12p40 fused to IL-p35 via a linker and a bispecific heterodimeric IgG Fc comprising at least one human IgG1 Fc “knob” and at least one IgG Fc “hole”.
- 5 14. The composition of claim 9, wherein said IL-12 variant polypeptide comprises dimeric IL-12 comprising said IL-12p40 and said IL-p35 and a bispecific heterodimeric IgG Fc comprising at least one human IgG1 Fc “knob” and at least one IgG Fc “hole”.
- 10 15. A composition comprising a nucleic acid molecule encoding said IL-12p40 according to any one of claims 1 to 14.
- 15 16. The composition of claim 15, further comprising a nucleic acid molecule encoding a p35 subunit (IL-12p35) with or without a signal peptide comprising an amino acid sequence selected from a group consisting of SEQ ID NO: 2 , SEQ ID NO: 30 and SEQ ID NO: 35 or wherein the nucleic acid molecule encoding the IL-12p40 further encodes the IL-12p35.
- 20 17. A composition of any one of claims 1 to 16 for use in treating or preventing a disease or disorder in a subject in need thereof.
18. The composition for use of claim 17, wherein said disease or disorder is cancer.
- 25 19. The composition for use of claim 17 or 18, comprising administering said IL-12 variant polypeptide via:
- a) a lipid nanoparticle encapsulated mRNA molecule encoding said IL-12 variant polypeptide;
 - b) a viral vector expressing said IL-12 variant polypeptide; or
 - c) an engineered immune cell expressing said IL-12 variant polypeptide.
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20. Use of a p40 subunit (IL-12p40) with or without a signal peptide or a nucleic acid encoding said IL-12p40 for the manufacture of a medicament for the treatment or prevention of cancer, wherein the IL-12p40 comprises mutations H216X, K217X, and K219X, relative to SEQ ID NO: 1, wherein X represents any amino acid.