

What is claimed is:

1. An isolated soluble fusion protein complex comprising at least two soluble proteins, wherein
the first soluble protein comprises an interleukin-15 (IL-15) polypeptide domain and the second soluble protein comprises a soluble IL-15 receptor alpha sushi-binding domain (IL-15R α Su) fused to an immunoglobulin Fc domain,
wherein one of the first or second soluble protein further comprises a binding domain that specifically binds to a disease antigen, immune checkpoint molecule or immune signaling molecule, and
wherein the IL-15 domain of the first soluble protein binds to the IL-15R α Su domain of the second soluble protein to form a soluble fusion protein complex.
2. The soluble fusion protein complex of claim 1, wherein one of the first or second soluble protein further comprises a second binding domain that specifically binds to a disease antigen, immune checkpoint molecule, or immune signaling molecule.
3. The soluble fusion protein complex of claim 1, wherein the IL-15 polypeptide is an IL-15 variant comprising an N72D mutation (IL-15N72D).
4. The soluble fusion protein complex of claim 1 or 2, wherein the binding domain comprises an immunoglobulin light chain variable domain covalently linked to an immunoglobulin heavy chain variable domain by a polypeptide linker sequence.
5. The soluble fusion protein complex of claim 1, wherein the binding domain specifically binds to one or more molecules comprising: programmed death ligand 1 (PD-L1), programmed death 1 (PD-1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), cluster of differentiation 33 (CD33), cluster of differentiation 47 (CD47), glucocorticoid-induced tumor necrosis factor receptor (TNFR) family related gene (GITR), lymphocyte function-associated antigen 1 (LFA-1), tissue factor (TF), delta-like protein 4 (DLL4), single strand DNA or T-cell immunoglobulin and mucin-domain containing-3 (Tim-3).
6. The soluble fusion protein complex of claim 5, wherein the first soluble protein comprises the amino acid sequence set forth in one of SEQ ID NOs: 2, 6, 10, 18, 20, 24, 28, 32, or 38.

7. The soluble fusion protein complex of claim 5, wherein the second soluble protein comprises the amino acid sequence set forth in one of SEQ ID NOs: 4, 8, 12, 14, 16, 22, 26, 30, 34, 36, 40, 42, 44, 46, 51, 52, 53, or 54.

8. A soluble fusion protein complex comprising a first soluble fusion protein complex of claim 1 covalently linked to a second soluble fusion protein complex of claim 1.

9. The soluble fusion protein complex of claim 8, wherein the first soluble fusion protein complex is covalently linked to the second soluble fusion protein complex by a disulfide bond linking the Fc domain of the first soluble fusion protein complex to the Fc domain of the second soluble fusion protein complex.

10. A nucleic acid sequence encoding the first soluble protein of claim 6, wherein said nucleic acid sequence comprises the sequence set forth in one of SEQ ID NOs: 1, 5, 9, 17, 19, 23, 27, 31 or 37.

11. The nucleic acid sequence of claim 10, wherein the nucleic acid sequence further comprises a promoter, translation initiation signal, and leader sequence operably linked to the sequence encoding the soluble protein.

12. A nucleic acid sequence encoding the second soluble protein of claim 7, wherein said nucleic acid sequence comprises the sequence set forth in one of SEQ ID NOs: 3, 7, 11, 13, 15, 21, 25, 29, 33, 35, 39, 41, 43, 45, 47, 48, 49, or 50.

13. The nucleic acid sequence of claim 12, wherein the nucleic acid sequence further comprises a promoter, translation initiation signal, and leader sequence operably linked to the sequence encoding the soluble protein.

14. A DNA vector comprising the nucleic acid sequences of claim 11 and/or claim 13.

15. The soluble fusion protein complex of claim 1 or 2, wherein the disease antigen is associated with neoplasia, infectious disease, or autoimmune disease.

16. The isolated soluble fusion protein complex of any one of claims 1-9 for use in therapy.

17. Use of an effective amount of a pharmaceutical composition comprising the soluble fusion protein complex of any one of claims 1 to 9 or 15 in the preparation of a medicament for the treatment of a neoplasia, infectious disease or autoimmune disease in a subject in need thereof.

18. The use of claim 17, wherein said neoplasia is selected from the group consisting of a glioblastoma, prostate cancer, hematological cancer, B-cell neoplasms, multiple myeloma, B-cell lymphoma, B cell non-Hodgkin lymphoma, Hodgkin's lymphoma, chronic lymphocytic leukemia, acute myeloid leukemia, cutaneous T-cell lymphoma, T-cell lymphoma, a solid tumor, urothelial/bladder carcinoma, melanoma, lung cancer, renal cell carcinoma, breast cancer, gastric and esophageal cancer, prostate cancer, pancreatic cancer, colorectal cancer, ovarian cancer, non-small cell lung carcinoma, and squamous cell head and neck carcinoma.

19. The use of claim 17 or 18, wherein said effective amount is between about 1 and 100 µg/kg said fusion protein complex.

20. The use of claim 17 or 18, wherein said fusion protein complex is to be administered at least one time per week.

21. The use of any one of claims 17 to 20, wherein said pharmaceutical composition is to be administered systemically, locally, intravenously, subcutaneously or intratumorally.

22. The use of any one of claims 17 to 21, wherein said fusion protein complex induces an immune response in the subject.

23. The use of any one of claims 17 to 22, wherein said fusion protein complex increases immune cell proliferation.

24. The use of any one of claims 17 to 23, wherein said fusion protein complex stimulates immune cell responses against cells associated with said neoplasia, infectious disease or autoimmune disease.

25. A nucleic acid sequence comprising SEQ ID NOS. 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 48, 49 or 50.

26. A peptide comprising SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 51, 52, 53 or 54.

27. Use of a composition comprising a therapeutically effective amount of a soluble fusion protein complex comprising SEQ ID NOS: 51, 52, 53 or 54 in the preparation of a medicament for the prevention or treatment of a human immunodeficiency virus (HIV) infection.

28. A pharmaceutical composition comprising the isolated soluble fusion protein complex of claims 1-9 or 15, the nucleic acid sequence of claims 10, 12 or 25, the DNA vector of claim 14, or the peptide sequence of claim 26.