

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 at least 95% identical to SEQ ID NO:2 or SEQ ID NO:6, 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 or immune checkpoint 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, 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. The isolated soluble fusion protein complex of any one of claims 1-7 for use in therapy.

9. Use of an effective amount of a pharmaceutical composition comprising the soluble fusion protein complex of any one of claims 1 to 7 in the preparation of a medicament for the treatment of a neoplasia, infectious disease or autoimmune disease in a subject in need thereof.

10. The use of claim 9, 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.

11. The use of claim 9 or 10, wherein said effective amount is between about 1 and 100 µg/kg said fusion protein complex.

12. The use of claim 9 or 10, wherein said fusion protein complex is to be administered at least one time per week.

13. The use of any one of claims 9 to 12, wherein said pharmaceutical composition is to be administered systemically, locally, intravenously, subcutaneously or intratumorally.

14. The use of any one of claims 9 to 13, wherein said fusion protein complex induces an immune response in the subject.

15. The use of any one of claims 9 to 14, wherein said fusion protein complex increases immune cell proliferation.

16. The use of any one of claims 9 to 15, wherein said fusion protein complex stimulates immune cell responses against cells associated with said neoplasia, infectious disease or autoimmune disease.

17. A pharmaceutical composition comprising the isolated soluble fusion protein complex of any one of claims 1-7.

18. An isolated soluble fusion protein comprising IL-15 peptide domain fused to a binding domain at least 95% identical to SEQ ID NO:2 or SEQ ID NO:6.

19. An isolated soluble fusion protein comprising IL-15R α Su fused to both: (a) an immunoglobulin Fc domain; and (b) a binding domain at least 95% identical to SEQ ID NO:2 or SEQ ID NO:6.