

CLAIMS

WHAT IS CLAIMED IS:

1. An immunomodulatory fusion protein comprising:
 - (i) an IL-2;
 - 5 (ii) an IL-12;
 - (iii) a collagen-binding domain, wherein the collagen-binding domain comprises a leucine-rich repeat from a human proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family; or a human type I glycoprotein having an Ig-like domain, and
 - 10 (iv) a linear polypeptide spacer.
2. The immunomodulatory fusion protein of claim 1, wherein the fusion protein is linear, a continuous chain, or a continuous polypeptide chain.
3. The immunomodulatory fusion protein of claim 1 or claim 2, wherein the IL-2 is at the N-terminus and the IL-12 is at the C-terminus.
- 15 4. The immunomodulatory fusion protein of any one of claims 1-3, wherein the linear polypeptide spacer is positioned in between the IL-2 and the collagen-binding domain and/or the collagen-binding domain is positioned in between the IL-12 and the linear polypeptide spacer.
5. The immunomodulatory fusion protein of any one of claims 1-4, further comprising a second linear polypeptide spacer.
- 20 6. The immunomodulatory fusion protein of claim 5, wherein the IL-12 is at the N terminus and is operably linked to the first linear polypeptide spacer, which is operably linked to the collagen binding domain, which is operably linked to the second linear polypeptide spacer, which is operably linked to the IL-2 at the C terminus of the protein, and wherein the protein is linear or the IL-12 is at the C terminus and is operably linked to the first linear polypeptide spacer, which
- 25 is operably linked to the collagen binding domain, which is operably linked to the second linear polypeptide spacer, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.
7. The immunomodulatory fusion protein of claim 5, wherein the IL-12 is at the C terminus and is operably linked to the first linear polypeptide spacer, which is operably linked to the
- 30 collagen binding domain, which is operably linked to the second linear polypeptide spacer, which is operably linked to the IL-2 at the N terminus of the protein, and wherein the protein is linear.

8. The immunomodulatory fusion protein of any one of claims 1 to 7, wherein the leucine-rich repeat from a human proteoglycan Class II member of the small leucine-rich proteoglycan (SLRP) family comprises lumican.
9. The immunomodulatory fusion protein of claim 8, wherein the lumican comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 11.
10. The immunomodulatory fusion protein of any one of claims 1 to 9, wherein the human type I glycoprotein having an Ig-like domain is LAIR 1.
11. The immunomodulatory fusion protein of claim 10, wherein LAIR1 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 13 or SEQ ID NO: 14.
12. The immunomodulatory fusion protein of any one of claims 1 to 9, wherein the human type I glycoprotein having an Ig-like domain is LAIR 2.
13. The immunomodulatory fusion protein of claim 12, wherein LAIR2 comprises at least 80% identity to the amino acid sequence as set forth in SEQ ID NO: 15.
14. The immunomodulatory fusion protein of any one of claims 1-13, wherein the IL-2 comprises human IL-2 or human wild-type IL-2.
15. The immunomodulatory fusion protein of any one of claims 1-14, wherein the IL-2 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2.
16. The immunomodulatory fusion protein of any one of claims 1-15, wherein the IL-12 comprises human IL-12 or human wild-type IL-12.
17. The immunomodulatory fusion protein of any one of claims 1-16, wherein the IL-12 comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 5 or SEQ ID NO: 6.
18. The immunomodulatory fusion protein of any one of claims 1-17, wherein the linear polypeptide spacer is an albumin or an albumin binding domain.
19. The immunomodulatory fusion protein of claim 18, wherein the albumin comprises human albumin or human serum albumin.
20. The immunomodulatory fusion protein of claim 18 or claim 19, wherein the albumin comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NOs: 16-18 or the albumin binding domain comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 19.
21. The immunomodulatory fusion protein of any one of claims 1-20, wherein the immunomodulatory fusion protein has a molecular weight of about 100 – about 1000 kDa.

22. A pharmaceutical composition comprising an immunomodulatory fusion protein of any one of claims 1-21, and a pharmaceutically acceptable carrier.
23. Use of the immunomodulatory fusion protein of any one of claims 1 – 21 in the manufacture of a pharmaceutical composition for activating, enhancing or promoting a response
5 by an immune cell in a subject or inhibiting, reducing or suppressing a response by an immune cell in a subject, or treating cancer, or reducing or inhibiting tumor growth.
24. The use of claim 23, wherein the subject has at least one tumor, and the composition is to be administered intratumorally (i.tu) peritum orally (peri.tu), or by injection to the at least one tumor.
- 10 25. The use of claim 24, wherein the at least one tumor size is reduced or substantially identical to a reference standard, including wherein the reference standard is the size of the tumor prior to administration.
26. The use of claim 24, wherein the composition has an intratumoral retention $t_{1/2}$ of more than 24 hours, including wherein twelve hours after intratumoral injection less than 25% of the
15 injected dose is detected in the serum.
27. The use of any one of claims 24 to 25, wherein the at least one tumor has stromal CD8+ cytotoxic T cells (CTL) ≤ 50 cells/mm² and/or intraepithelial compartment CD8+ cytotoxic T cells (CTL) < 500 cells/mm².
28. The use of any one of claims 24 to 27, wherein the method does not result in cytokine
20 release syndrome in the subject, including wherein the subject does not experience grade 4 cytokine release syndrome.
29. Use of the immunomodulatory fusion protein of any one of claims 1 – 21 in the manufacture of a pharmaceutical composition for reducing or inhibiting tumor growth or treating cancer in a subject in combination with a second composition comprising (i) a tumor antigen-
25 targeting antibody, (ii) a cancer vaccine, (iii) an immune checkpoint inhibitor, or (iv) an adoptive cell therapy, thereby reducing or inhibiting tumor growth or treating cancer in the subject.
30. The use of claim 29, wherein the tumor antigen is a tumor-associated antigen (TAA), a tumor specific antigen (TSA), or a tumor neoantigen and/or wherein the tumor antigen-targeting antibody specifically binds human HER-2/neu, EGFR, VEGFR, CD20, CD33, CD38 or antigen-
30 binding fragment thereof, or

wherein the cancer vaccine is a peptide comprising one or more tumor-associated antigens, or a population of cells immunized in vitro with a tumor antigen and administered to the subject, or

wherein the immune checkpoint inhibitor is an antibody or antigen binding fragment thereof which binds PD-1, PD-L1, CTLA-4, LAG3, or TIM3, or

wherein the immune effector cell comprises a chimeric antigen receptor (CAR) molecule which binds to a tumor antigen.

- 5 31. An immunomodulatory fusion protein comprising:
- (i) an IL-2;
 - (ii) an IL-12;
 - (iii) a LAIR2 collagen-binding domain,
- 10 wherein LAIR2 comprises at least 80% identity to the amino acid sequence as set forth in SEQ ID NO: 15; and
- (iv) an albumin;
- wherein the albumin comprises at least about 80% sequence identity to the amino acid sequence as set forth in SEQ ID NO: 16-18.