

CLAIMS

1. A multimeric protein comprising at least three monomer polypeptides, wherein each monomer polypeptide comprises (1) a first 4-1BB-targeting moiety (T1), and (2) an oligomerization moiety (O).
2. The multimeric protein of claim 1, wherein the first 4-1BB-targeting moiety (T1) is fused at its N-terminus or C-terminus to the C-terminus or N-terminus, respectively, of the oligomerization moiety (O) via a linker (L).
3. The multimeric protein of claim 1 or 2, wherein the monomer polypeptide comprises at least one additional targeting moiety (T2).
4. The multimeric protein of any one of claims 1-3, wherein the monomer polypeptide comprises an additional targeting moiety (T2), wherein the additional targeting moiety is placed in tandem with the first 4-1BB-targeting moiety (T1).
5. The multimeric protein of claim 4, wherein the monomer polypeptide has one of the following configurations:
 - a. T1-L'-T2-L-O;
 - b. T2-L'-T1-L-O;
 - c. O-L-T1-L'-T2; or
 - d. O-L-T2-L'-T1

wherein L' is a linker that is the same as or different from L.

6. The multimeric protein of any one of claims 1-3, wherein the monomer polypeptide comprises an additional targeting moiety (T2), wherein the additional targeting moiety (T2) is linked to a different terminus of the oligomerization moiety (O) than the first 4-1BB-targeting moiety (T1).
7. The multimeric protein of claim 6, wherein the monomer polypeptide has one of the following configurations:
 - a. T1-L-O-L'-T2; or
 - b. T2-L'-O-L-T1

wherein L' is a linker that is the same as or different from L.

8. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a second 4-1BB-targeting moiety.
9. The multimeric protein of claim 8, wherein the second 4-1BB-targeting moiety is the same as the first 4-1BB-targeting moiety (T1).
10. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a moiety that targets a tumor associated antigen.
11. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a moiety that targets a tumor associated antigen and is a lipocalin mutein.
12. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a moiety that targets a tumor associated antigen and is an antibody or an antigen-binding domain or derivative thereof.
13. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a moiety that targets a tumor associated antigen and is a single chain variable fragment (scFv).
14. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a GPC3-targeting moiety.
15. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a GPC3-targeting moiety that is a lipocalin mutein.
16. The multimeric protein of claim 15, wherein the lipocalin mutein has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 74-97.
17. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a GPC3-targeting moiety that is an antibody or an antigen-binding domain or derivative thereof.
18. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a GPC3-targeting moiety that is a single chain variable fragment (scFv).
19. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a PD-L1-targeting moiety.
20. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a PD-L1-targeting moiety that is a single chain variable fragment (scFv).

21. The multimeric protein of claim 20, wherein the scFv has at least 85% sequence identity to the amino acid sequence shown in SEQ ID NO: 172.
22. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a T cell activation enhancing targeting moiety.
23. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a T cell activation enhancing targeting moiety that is a lipocalin mutein.
24. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a T cell activation enhancing targeting moiety that is an antibody or an antigen-binding domain or derivative thereof.
25. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is a T cell activation enhancing targeting moiety that is a single chain variable fragment (scFv).
26. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is an OX40-targeting moiety.
27. The multimeric protein of any one of claims 3-7, wherein the additional targeting moiety (T2) is an OX40-targeting moiety that is a lipocalin mutein.
28. The multimeric protein of claim 27, wherein the lipocalin mutein has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 174-202.
29. The multimeric protein of any one of claims 1-28, wherein the first 4-1BB-targeting moiety (T1) is a lipocalin mutein.
30. The multimeric protein of any one of claims 1-29, wherein the first 4-1BB-targeting moiety (T1) is a lipocalin mutein having at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 56-71.
31. The multimeric protein of any one of claims 1-30, wherein the oligomerization moiety (O) is capable of promoting trimerization.
32. The multimeric protein of any one of claims 1-31, wherein the oligomerization moiety (O) is a trimerization domain of a collagen.
33. The multimeric protein of any one of claims 1-32, wherein the oligomerization moiety (O) has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 35-37.

34. The multimeric protein of any one of claims 1-33, wherein the multimeric protein is a trimeric protein.
35. The multimeric protein of any one of claims 1-30 and 33, wherein the multimeric protein is a tetrameric protein.
36. The multimeric protein of any one of claims 2-35, wherein the linker (L) has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 12-28.
37. The multimeric protein of any one of claims 1-36, wherein the multimeric protein has at least 85% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 38-55 and 164-167.
38. The multimeric protein of any one of claims 1-37, wherein the multimeric protein comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 38-55 and 164-167.
39. The multimeric protein of any one of claims 1-38, wherein the multimeric protein is capable of binding 4-1BB with a K_D value of about 0.68 nM or lower.
40. The multimeric protein of any one of claims 1-39, wherein the multimeric protein is capable of binding 4-1BB with an apparent K_D value lower than the K_D value of the 4-1BB-targeting lipocalin mutein that is included in the monomer polypeptide.
41. The multimeric protein of claim 39 or 40, wherein the apparent K_D value is determined by surface plasmon resonance (SPR).
42. The multimeric protein of any one of claims 1-41, wherein the multimeric protein is cross-reactive with cynomolgus 4-1BB.
43. A nucleic acid molecule comprising a nucleotide sequence encoding a monomer polypeptide comprised in a multimeric protein of any one of claims 1-42.
44. The nucleic acid molecule of claim 43, wherein the nucleic acid molecule is operably linked to a regulatory sequence to allow expression of said nucleic acid molecule.
45. The nucleic acid molecule of claim 43 or 44, wherein the nucleic acid molecule is comprised in a vector or in a phagemid vector.
46. The nucleic acid molecule of any one of claims 43 or 44, wherein the nucleic acid molecule is comprised in a viral vector, in a nanoparticle, or a liposome.

47. The nucleic acid molecule of any one of claims 43-46, wherein the nucleic acid molecule is comprised in the genomic DNA of a host cell.
48. A cell containing a nucleic acid molecule of any one of claims 43-47 and/or expressing the multimeric protein of any one of claims 1-42 and/or expressing a monomer polypeptide as defined in any one of claims 1-42.
49. The cell of claim 48, wherein the cell secretes the multimeric protein and/or the monomer polypeptide.
50. The cell of claim 48, wherein the cell secretes the monomer polypeptide.
51. The cell of claim 50, wherein the monomer polypeptide self-assembles to a multimeric protein after secretion.
52. The cell of any one of claims 48-51, wherein the cell is an immune cell.
53. The cell of claim 52, wherein the cell is a T cell.
54. The cell of claim 53, wherein the cell is a CD8+ T cell.
55. The cell of claim 53, wherein the cell is a CD4+ T cell.
56. The cell of any one of claims 52-55, wherein the cell comprises a recombinant antigen receptor.
57. The cell of claim 56, wherein the recombinant antigen receptor is a chimeric antigen receptor (CAR).
58. The cell of claim 56, wherein the recombinant antigen receptor is a T cell receptor (TCR).
59. The cell of any one of claims 52-57, wherein the cell is a CAR-T cell.
60. The cell of any one of claims 52-59, wherein the cell expresses 4-1BB.
61. The cell of any one of claims 52-60, wherein the cell is a human cell.
62. A method of producing the multimeric protein of any one of claims 1-42, wherein the multimeric protein is produced starting from the nucleic acid coding for the monomer polypeptides comprised in the multimeric protein.
63. The method of claim 62, wherein the multimeric protein is produced in a bacterial or eukaryotic host organism.

64. A use of the multimeric protein of any one of claims 1-42 or a composition comprising such multimeric protein or a cell of any one of claims 48-61 for inducing 4-1BB (and/or, optionally, OX40) clustering and activation on T cells.
65. A use of the multimeric protein of any one of claims 1-42 or a composition comprising such multimeric protein or a cell of any one of claims 48-61 for co-stimulating T cells and/or activating downstream signaling pathways of 4-1BB (and/or, optionally, OX40).
66. A use of the multimeric protein of any one of claims 1-42 or a composition comprising such multimeric protein or a cell of any one of claims 48-61 for co-stimulating T cells when engaging GPC3-expressing or PD-L1-expressing tumor cells.
67. The use of any one of claims 64-66, wherein the T cell is a T cell expressing the multimeric protein and/or one of its monomer polypeptides.
68. The use of any one of claims 64-66, wherein the T cell is a T cell not expressing the multimeric protein and/or one of its monomer polypeptides.
69. A pharmaceutical composition comprising one or more multimeric proteins of any one of claims 1-42 and/or one or more cells of any one of claims 48-61.
70. The multimeric protein of any one of claims 1-42 and/or the cell of any one of claims 48-61 for use in a therapy.
71. The multimeric protein and/or the cell for use of claim 70, wherein the use is in the treatment of cancer.
72. Use of a multimeric protein of any one of claims 1-42 and/or the cell of any one of claims 48-61 for the manufacture of a medicament.
73. The use of claim 72, wherein the medicament is for the treatment of cancer.