

CLAIMS

~~LISTING OF CLAIMS:~~

1. A fusion polypeptide, comprising:
an interleukin (IL) polypeptide;
a first TGF β superfamily receptor polypeptide; and
a second TGF β superfamily receptor polypeptide.
2. ~~A~~The fusion polypeptide of claim 1 comprising:
an IL polypeptide that binds to and agonizes an IL receptor; a first TGF β superfamily receptor polypeptide that binds to and sequesters soluble TGF β ; and a second TGF β superfamily receptor polypeptide that binds to and sequesters soluble TGF β .
3. The fusion polypeptide of any one of claims 1 to 2, wherein the IL polypeptide comprises an IL-2 polypeptide or IL-15.
- ~~4. The fusion polypeptide of any one of claims 1 to 3, wherein the IL polypeptide comprises an IL-2 polypeptide.~~
- ~~5. The fusion polypeptide of claim 4, wherein the IL-2 polypeptide comprises SEQ ID NO: 2 or SEQ ID NO: 3.~~
- ~~46. The fusion polypeptide of claim 34, wherein the IL-2 polypeptide comprises an amino acid sequence having greater than 80%, 85%, 90%, 95% 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 2, or an amino acid sequence having greater than 80%, 85%, 90%, 95% 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 3.~~
- ~~7. The fusion polypeptide of claim 4, wherein the IL-2 polypeptide consists of SEQ ID NO: 2 or SEQ ID NO: 3.~~
- ~~8. The fusion polypeptide of any one of claims 1 to 3, wherein the IL polypeptide comprises an IL-15 polypeptide.~~
- ~~9. The fusion polypeptide of claim 8, wherein the IL-15 polypeptide comprises SEQ ID NO: 5.~~
- ~~540. The fusion polypeptide of claim 38, wherein the IL-15 polypeptide comprises an amino acid sequence having greater than 80%, 85%, 90%, 95% 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 5.~~

~~11. The fusion polypeptide of claim 8, wherein the IL-15 polypeptide consists of SEQ ID NO: 5.~~

~~612.~~ The fusion polypeptide of any one of claims 1 to ~~511~~, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises an activin receptor polypeptide or fragment thereof, a bone morphogenetic protein (BMP) receptor polypeptide or fragment thereof, a glial cell-derived neurotrophic factor (GDNF) receptor polypeptide or fragment thereof, or a TGF β receptor II polypeptide or fragment thereof.

~~713.~~ The fusion polypeptide of any one of claims 1 to ~~612~~, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a TGF β receptor II (TBRII) polypeptide or fragment thereof, optionally:-

~~14. The fusion polypeptide of any one of claims 1 to 13,~~ wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a soluble TGF β receptor II (TBRII) polypeptide or fragment thereof.

~~815.~~ The fusion polypeptide of any one of claims 1 to ~~714~~, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a soluble TGF β receptor II (TBRII) polypeptide comprising SEQ ID NO: 8, SEQ ID NO: 9, or a combination thereof, optionally:-

~~16. The fusion polypeptide of any one of claims 1 to 15,~~ wherein the first TGF β superfamily receptor polypeptide comprises an amino acid sequence of SEQ ID NO: 8 and the second TGF β superfamily receptor polypeptide comprises a truncation of an amino acid sequence of SEQ ID NO: 9, optionally:-

~~17. The fusion polypeptide of any one of claims 14 to 16,~~ wherein the soluble TGF β receptor II polypeptide comprises an amino acid sequence having greater than 80%, 85%, 90%, 95% 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 8 or SEQ ID NO: 9.

~~918.~~ The fusion polypeptide of any one of claims 1 to ~~817~~, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide binds a TGF- β 1 polypeptide, a TGF- β 2 polypeptide, a TGF- β 3 polypeptide, a activin β A polypeptide, a activin β B polypeptide, a activin β C polypeptide, a activin β E polypeptide, a bone morphogenic protein (BMP) 2 polypeptide, a BMP 3 polypeptide, a BMP4 polypeptide, a BMP 5 polypeptide, a BMP 6 polypeptide, a BMP 7 polypeptide, a BMP 8 polypeptide, a BMP 9 polypeptide, a BMP 10

polypeptide, a BMP 11 polypeptide, a BMP 12 polypeptide, a BMP 13 polypeptide, a BMP 14 polypeptide, a BMP 15 polypeptide, a growth differentiation factor (GDF) 1 polypeptide, a GDF 3 polypeptide, a GDF 8 polypeptide, a GDF 9 polypeptide, a GDF 15 polypeptide, a Nodal polypeptide, a Inhibin α polypeptide, an anti-Mullerian Hormone polypeptide, a Lefty 1 polypeptide, a Lefty 2 polypeptide, an arteman polypeptide, a Persephin polypeptide, or a Neurturin polypeptide.

1049. The fusion polypeptide of any one of claims 1 to 948, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide binds a TGF β 1 polypeptide, a TGF β 2 polypeptide, a TGF β 3 polypeptide, or any combination thereof.

~~20.—The fusion polypeptide of any one of claims 1 to 19, wherein the first TGF β superfamily receptor polypeptide and the second TGF β superfamily receptor polypeptide binds a TGF β 1 polypeptide.~~

1124. The fusion polypeptide of any one of claims 1-1020, wherein the ~~truncated~~ TGF β superfamily receptor polypeptide comprises an N terminus truncation, a C terminus truncation, or combination thereof, optionally:-

~~22.—The fusion protein of claim 21, wherein the truncated TGF β superfamily receptor polypeptide is a truncated soluble TGF β receptor II (sT β RII) polypeptide.~~

~~23.—The fusion polypeptide of claim 22, wherein the truncation comprises greater than 2, 5, 7, 10, 15, 20, 25, or 30 amino acids.~~

1224. The fusion polypeptide of any one of claims 1 to 1123, wherein the IL polypeptide comprises a truncated IL polypeptide, optionally:-

~~25.—The fusion polypeptide of claim 24, wherein the truncated IL polypeptide comprises an N terminus truncation, a C terminus truncation, or combination thereof.~~

1326. The fusion polypeptide of claim 1224, wherein the truncated IL polypeptide comprises a truncated IL-2 polypeptide or IL-15 polypeptide.

1427. The fusion polypeptide of any one of claims 1 to 1326, ~~further~~ comprising a linker polypeptide or a linker molecule attaching the first TGF β superfamily receptor polypeptide and the second TGF β superfamily receptor polypeptide.

~~28.—The fusion polypeptide of any one of claims 1 to 27, further comprising a linker polypeptide fusing the IL polypeptide and the first TGF β superfamily receptor polypeptide.~~

1529. The fusion polypeptide of any one of claims 1 to ~~1428~~, further comprising a pharmacokinetic (PK) modulator:

~~30. The fusion polypeptide of claim 29, wherein the pharmacokinetic modulator comprises an immunoglobulin constant (Fc) region polypeptide.~~

~~31. The fusion polypeptide of claim 30, wherein the immunoglobulin Fc region polypeptide is a human immunoglobulin Fc region polypeptide.~~

~~32. The fusion polypeptide of claim 30, wherein the immunoglobulin Fc region is an IgG Fc region.~~

~~33. The fusion polypeptide of claim 30, wherein the IgG Fc region is an IgG1, IgG2, IgG3, or IgG4 Fc region.~~

1634. The fusion polypeptide of claim 1529, wherein the PK modulator comprises an albumin polypeptide.

~~35. The fusion polypeptide of claim 34, wherein the albumin polypeptide is a human albumin polypeptide.~~

1736. The fusion polypeptide of any one of claims 1 to 1635, wherein the fusion polypeptide comprises an amino acid sequence having at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% sequence identity to any one of SEQ ID NOs: 10-25.

~~37. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 10.~~

~~38. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 11.~~

~~39. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 12.~~

~~40. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 13.~~

~~41. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 14.~~

~~42. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 15.~~

- ~~43. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 16.~~
- ~~44. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 17.~~
- ~~45. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 18.~~
- ~~46. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 19.~~
- ~~47. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 20.~~
- ~~48. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 21.~~
- ~~49. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 22.~~
- ~~50. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 23.~~
- ~~51. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 24.~~
- ~~52. The fusion polypeptide of claim 36, wherein the fusion polypeptide comprises an amino acid sequence of SEQ ID NO: 25.~~
- ~~53. The fusion polypeptide of any one of claims 1 to 52, wherein the fusion polypeptide consists of any one of SEQ ID NOs: 10-25.~~
1854. The fusion polypeptide of any one of claims 1 to 17-53, wherein the fusion polypeptide activates target cells expressing an IL-2 or IL-15 receptor, optionally:-
- ~~55. The fusion polypeptide of claim 54, wherein the target cell is an immune cell, optionally:-~~
- ~~56. The fusion polypeptide of claim 55, wherein the immune cell is a T cells, natural killer cell,s NKT cells, B cells, or gamma delta T cells.~~
- ~~57. A pharmaceutical composition comprising the fusion polypeptide of any one of claims 1 to 56, comprising a pharmaceutically acceptable carrier or excipient.~~

~~58. — A method of inhibiting or reducing tumor growth and/or progression in an individual having cancer, comprising administering to the individual a fusion polypeptide comprising:~~

~~(a) an interleukin (IL) polypeptide;~~

~~(b) a first TGF β superfamily receptor polypeptide; and~~

~~(c) a second TGF β superfamily receptor polypeptide;~~

~~thereby inhibiting or reducing tumor growth and/or progression in the individual.~~

~~59. — The method of claim 58, wherein the tumor is a primary tumor.~~

~~60. — The method of any one of claims 58 to 59, wherein the tumor is a metastatic tumor.~~

~~61. — The method of any one of claims 58 to 60, wherein the cancer comprises a solid tumor.~~

~~62. — The method of any one of claims 58 to 61, wherein the fusion polypeptide activates immune cells within a tumor microenvironment.~~

~~63. — The method of claim 62, wherein the immune cells express IL-2.~~

~~64. — The method of claim 63, wherein the immune cells comprise T cells, natural killer cells, NKT cells, B cells, or gamma delta T cells.~~

~~65. — The method of any one of claims 58 to 64, wherein the fusion polypeptide inhibits or reduces immunosuppression of immune cells within a tumor microenvironment and/or reduces or inhibits the activation of immunosuppressive cells in the tumor microenvironment.~~

~~66. — The method of any one of claims 58 to 65, wherein the cancer is a hematological cancer.~~

~~67. — The method of any one of claims 58 to 66, wherein the cancer a cancer comprising a solid tumor.~~

~~68. — A method of neutralizing or killing tumor cells in an individual having cancer, comprising administering to the individual a fusion polypeptide comprising:~~

~~(a) an interleukin (IL) polypeptide;~~

~~(b) a first TGF β superfamily receptor polypeptide; and~~

~~(c) a second TGF β superfamily receptor polypeptide;~~

~~thereby neutralizing or killing tumor cells in the individual.~~

~~69. — The method of claim 68, wherein the tumor is a primary tumor.~~

~~70. — The method of any one of claims 68 to 69, wherein the tumor is a metastatic tumor.~~

~~71. — The method of any one of claims 68 to 70, wherein the cancer comprises a solid tumor.~~

72. — The method of any one of claims 68 to 71, wherein the fusion polypeptide activates immune cells within a tumor microenvironment.
73. — The method of claim 72, wherein the immune cells express IL-2 or IL-15 receptors.
74. — The method of claim 72, wherein the immune cells comprise T cells, natural killer cells, NKT cells, B cells, or gamma delta T cells.
75. — The method of any one of claims 68 to 74, wherein the fusion polypeptide inhibits or reduces immunosuppression of immune cell within a tumor microenvironment and/or reduces or inhibits the activation of immunosuppressive cells in the tumor microenvironment.
76. — The method of any one of claims 68 to 75, wherein the cancer is a hematological cancer.
77. — The method of any one of claims 68 to 76, wherein the cancer comprises a solid tumor.
78. — A method of treating or ameliorating cancer in a subject having a cancer, comprising administering to the subject a fusion polypeptide comprising a
- (a) an interleukin (IL) polypeptide;
 - (b) a first TGF β superfamily receptor polypeptide; and
 - (c) a second TGF β superfamily receptor polypeptide;
- thereby treating or ameliorating the cancer in the subject.
79. — The method of claim 78, wherein the tumor is a primary tumor.
80. — The method of any one of claims 78 to 79, wherein the tumor is a metastatic tumor.
81. — The method of any one of claims 78 to 80, wherein the cancer comprises a solid tumor.
82. — The method of any one of claims 78 to 81, wherein the fusion polypeptide activates immune cells within a tumor microenvironment.
83. — The method of claim 82, wherein the immune cells express IL-2 or IL-15 receptors.
84. — The method of claim 82, wherein the immune cells comprise T cells, natural killer cells, NKT cells, B cells, or gamma delta T cells.
85. — The method of any one of claims 78 to 84, wherein the fusion polypeptide inhibits or reduces immunosuppression of immune cell within a tumor microenvironment and/or reduces or inhibits the activation of immunosuppressive cells in the tumor microenvironment.
86. — The method of any one of claims 78 to 85, wherein the cancer is a hematological cancer.
87. — The method of any one of claims 78 to 86, wherein the cancer comprises a solid tumor.

~~88. The method of any one of claims 78 to 87, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide binds a TGF β 1 polypeptide, a TGF β 2 polypeptide, a TGF β 3 polypeptide, or any combination thereof.~~

~~89. A method of activating a cell expressing an IL receptor comprising: contacting a cell with a fusion polypeptide comprising~~

~~(a) an interleukin (IL) polypeptide;~~

~~(b) a first TGF β superfamily receptor polypeptide; and~~

~~(c) a second TGF β superfamily receptor polypeptide.~~

~~90. The method of claim 89, wherein the cell is an immune cell.~~

~~91. The method of claim 90, wherein the immune cell comprises T cells, natural killer cells, NKT cells, B cells, or gamma delta T cells.~~

~~92. The method of any one of claims 89 to 91, wherein the immune cells are contacted in vivo.~~

~~93. The method of any one of claims 89 to 91, wherein the immune cells are contacted ex vivo.~~

~~94. The method of claim 93, wherein a leukopak or leukapheresis product comprises the immune cells.~~

~~95. The method of claim 93, wherein the immune cells are derived from an apheresis sample.~~

~~96. The method of claim 93, wherein the immune cells are subsequently used for a cell-based therapy.~~

~~97. The method of any one of claims 89 to 96, wherein the IL polypeptide is IL 2 or IL 15.~~

~~98. The method of any one of claims 89 to 97, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a soluble TGF β receptor II (TBRII) polypeptide or fragment.~~

~~99. A host cell, comprising a nucleic acid molecule comprising a nucleic acid sequence encoding the recombinant fusion polypeptide as in any of claims 1 to 56.~~

19400. Use of the fusion polypeptide of any one of claims 1 to 18-56, in the manufacture of a medicament for inhibiting or reducing tumor growth and/or progression in an individual having cancer, optionally wherein the fusion polypeptide inhibits or reduces immunosuppression of

immune cell within a tumor microenvironment and/or reduces or inhibits the activation of immunosuppressive cells in the tumor microenvironment.

~~101. Use of the fusion polypeptide of any one of claims 1 to 56, for neutralizing or killing tumor cells in an individual having cancer.~~

~~102. Use of the fusion polypeptide of any one of claims 1 to 56, for treating or ameliorating cancer in a subject having a cancer.~~

~~20103. Use of the fusion polypeptide of any one of claims 1 to 18-56, in the manufacture of a medicament for activating a cell expressing an IL receptor, optionally wherein the fusion polypeptide inhibits or reduces immunosuppression of immune cell within a tumor microenvironment and/or reduces or inhibits the activation of immunosuppressive cells in the tumor microenvironment.~~

~~104. Use of the fusion polypeptide of any one of claims 1 to 56, in the manufacture of a medicament for inhibiting or reducing tumor growth and/or progression in an individual having cancer.~~

~~105. Use of the fusion polypeptide of any one of claims 1 to 56, in the manufacture of a medicament for neutralizing or killing tumor cells in an individual having cancer.~~

~~106. Use of the fusion polypeptide of any one of claims 1 to 56, in the manufacture of a medicament for treating or ameliorating cancer in a subject having a cancer.~~

~~107. Use of the fusion polypeptide of any one of claims 1 to 56, in the manufacture of a medicament for activating a cell expressing an IL receptor.~~

~~108. The fusion polypeptide of any one of claims 1 to 56, for use in inhibiting or reducing tumor growth and/or progression in an individual having cancer.~~

~~109. The fusion polypeptide of any one of claims 1 to 56, for use in neutralizing or killing tumor cells in an individual having cancer.~~

~~110. The fusion polypeptide of any one of claims 1 to 56, for use in treating or ameliorating cancer in a subject having a cancer.~~

~~111. The fusion polypeptide of any one of claims 1 to 56, for use in activating a cell expressing an IL receptor.~~