

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. 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 claim 3, 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.
5. The fusion polypeptide of claim 3, 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.
6. The fusion polypeptide of any one of claims 1 to 5, 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.
7. The fusion polypeptide of any one of claims 1 to 6, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a TGF β receptor II (TBR II) polypeptide or fragment thereof, optionally
wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a soluble TGF β receptor II (TBR II) polypeptide or fragment thereof.
8. The fusion polypeptide of any one of claims 1 to 7, wherein the first TGF β superfamily receptor polypeptide and/or the second TGF β superfamily receptor polypeptide comprises a

soluble TGF β receptor II (TBR II) polypeptide comprising SEQ ID NO: 8, SEQ ID NO: 9, or a combination thereof, optionally

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

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.

9. The fusion polypeptide of any one of claims 1 to 8, 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 artaman polypeptide, a Persephin polypeptide, or a Neurturin polypeptide.

10. The fusion polypeptide of any one of claims 1 to 9, 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.

11. The fusion polypeptide of any one of claims 1-10, wherein the TGF β superfamily receptor polypeptide comprises an N terminus truncation, a C terminus truncation, or combination thereof, optionally

wherein the truncation comprises greater than 2, 5, 7, 10, 15, 20, 25, or 30 amino acids.

12. The fusion polypeptide of any one of claims 1 to 11, wherein the IL polypeptide comprises a truncated IL polypeptide, optionally

wherein the truncated IL polypeptide comprises an N terminus truncation, a C terminus truncation, or combination thereof.

13. The fusion polypeptide of claim 12, wherein the truncated IL polypeptide comprises a truncated IL-2 polypeptide or IL-15 polypeptide.

14. The fusion polypeptide of any one of claims 1 to 13, comprising a linker polypeptide or a linker molecule attaching the first TGF β superfamily receptor polypeptide and the second TGF β superfamily receptor polypeptide.

15. The fusion polypeptide of any one of claims 1 to 14, comprising a pharmacokinetic (PK) modulator, wherein the pharmacokinetic modulator comprises an immunoglobulin constant (Fc) region polypeptide.

16. The fusion polypeptide of claim 15, wherein the PK modulator comprises an albumin polypeptide.

17. The fusion polypeptide of any one of claims 1 to 16, 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.

18. The fusion polypeptide of any one of claims 1 to 17, wherein the fusion polypeptide activates target cells expressing an IL-2 or IL-15 receptor, optionally wherein the target cell is an immune cell, optionally

wherein the immune cell is a T cell, natural killer cell, NKT cell, B cell, or gamma delta T cell.

19. Use of the fusion polypeptide of any one of claims 1 to 18 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.

20. Use of the fusion polypeptide of any one of claims 1 to 18 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.