

CLAIMS

What is claimed is:

1. A polypeptide construct useful to inhibit an effect of a Transforming Growth Factor Beta (TGF β) isoform, the construct comprising:

a TGF β -binding region, and

a multimerization domain;

wherein the N-terminus of the multimerization domain is joined to the C-terminus of the TGF β -binding region;

wherein the TGF β -binding region comprises, in an N- to C- terminal orientation, an N-terminal region, a first TGF β receptor ligand-binding domain (TGF β R-LBD), a first linker, a second TGF β R ligand-binding domain, and a second linker;

wherein the inhibitory potency of the polypeptide construct for both TGF β 1 isoform activity and TGF β 3 isoform activity is greater than for TGF β 2 isoform activity; and

wherein the first linker and the second linker are selected so that the relative inhibitory potency of the polypeptide construct for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio for TGF β 3:TGF β 1) is about 2.5:1 or less.

2. The polypeptide construct of claim 1, wherein the relative inhibitory potency of the polypeptide construct for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio for TGF β 3:TGF β 1) is: less than about 2.5:1, about 2.3:1 or less, about 2:1 or less, about 1.8:1 or less, about 1.5:1 or less, about 1.3:1 or less, about 1:1 or less, about 1:1 or less, about 0.8:1 or less, or about 0.5:1 or less.

3. The polypeptide construct of claim 1 or 2, wherein the relative inhibitory potency of the polypeptide construct for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio for TGF β 3:TGF β 1) is from about 1:1 to about 2:1.

4. The polypeptide construct of claim 3, wherein the relative inhibitory potency of the polypeptide construct for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio for TGF β 3:TGF β 1) is about 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, or 1.9:1.

5. The polypeptide construct of claim 4, wherein the relative inhibitory potency of the polypeptide construct for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio for TGF β 3:TGF β 1) is from about 1.4:1 to about 1.6:1.
6. The polypeptide construct of claim 5, wherein the relative inhibitory potency of the polypeptide construct for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio for TGF β 3:TGF β 1) is about 1.4:1, about 1.5:1, or about 1.6:1.
7. The polypeptide construct of any one of claims 1 to 6, wherein the polypeptide construct inhibits both TGF β 1 isoform activity and TGF β 3 isoform activity with at least 20-fold, 100-fold, 200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, 900-fold, or 1000-fold greater potency than TGF β 2 isoform activity.
8. The polypeptide construct of any one of claims 1 to 7, wherein the first linker is 33 amino acids or shorter.
9. The polypeptide construct of any one of claims 1 to 8, wherein the second linker is 10 amino acids or longer.
10. The polypeptide construct of any one of claims 1 to 9, wherein one or more of the first linker and the second linker comprises or consists of an IDR linker, an IDR linker variant, a hybrid linker, a hybrid linker variant, a truncated linker, a truncated linker variant or an elongated linker.
11. The polypeptide construct of claim 10, wherein one of the first linker and the second linker comprises or consists of a non-IDR linker.
12. The polypeptide construct of any one of claims 1 to 10, wherein both the first linker portion and the second linker portion comprise or consist of an IDR linker, an IDR linker variant, a hybrid linker, a hybrid linker variant, a truncated linker, a truncated linker variant or an elongated linker.
13. The polypeptide construct of any one of claims 1 to 12, wherein the first linker is 10 amino acids or longer, 15 amino acids or longer, or 18 amino acids or longer.
14. The polypeptide construct of any one of claims 1 to 13, wherein the first linker is from about 15 to 33 amino acids long, or from about 18 to about 30 amino acids long.

15. The polypeptide construct of any one of claims 1 to 14, wherein the first linker is about 16, about 18, about 30, or about 32 amino acids long.
16. The polypeptide construct of claim 15, wherein the first linker is 18 amino acids long.
17. The polypeptide construct of claim 15, wherein the first linker is 16 amino acids long.
18. The polypeptide construct of claim 15, wherein the first linker is 30 amino acids long.
19. The polypeptide construct of claim 15, wherein the first linker is 32 amino acids long.
20. The polypeptide construct of any one of claims 1 to 19, wherein the second linker is 35 amino acids or shorter, or from 10 to 34 amino acids long.
21. The polypeptide construct of any one of claims 1 to 20, wherein the second linker is from about 15 to about 35 amino acids long.
22. The polypeptide construct of any one of claims 1 to 21, wherein the second linker is about 16, about 30, about 32, or about 34 amino acids long.
23. The polypeptide construct of claim 22, wherein the second linker is 30 amino acids long.
24. The polypeptide construct of claim 22, wherein the second linker is 16 amino acids long.
25. The polypeptide construct of claim 22, wherein the second linker is 32 amino acids long.
26. The polypeptide construct of claim 22, wherein the second linker is 34 amino acids long.
27. The polypeptide construct of any one of claims 1 to 26, wherein one or more of the first linker and the second linker comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOs: 4 and 8-26, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.
28. The polypeptide construct of claim 27, wherein the first linker comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOs: 8, 9, 10, 11, 12, 13, 14, 16, 21, 22, 23, and 26, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.
29. The polypeptide construct of claim 27 or 28, wherein the second linker comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOs: 4, 9, 11, 15, 17, 18, 19,

20, 22, 23, 24, 25, and 26, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

30. The polypeptide construct of any one of claims 1 to 29, wherein the first linker comprises or consists of the amino acid sequence set forth in SEQ ID NO: 12.

31. The polypeptide construct of any one of claims 1 to 29, wherein the first linker comprises or consists of the amino acid sequence set forth in SEQ ID NO: 8.

32. The polypeptide construct of any one of claims 1 to 31, wherein the second linker comprises or consists of the amino acid sequence set forth in SEQ ID NO: 11.

33. The polypeptide construct of any one of claims 1 to 31, wherein the second linker comprises or consists of the amino acid sequence set forth in SEQ ID NO: 9.

34. The polypeptide construct of any one of claims 1 to 29, wherein the first linker comprises or consists of an amino acid sequence having:

(a) a deletion of at least one N-terminal amino acid residue in comparison with SEQ ID NO: 3, SEQ ID NO: 12 or SEQ ID NO: 8;

(b) a deletion of at least one C-terminal amino acid residue in comparison with SEQ ID NO: 3, SEQ ID NO: 12 or SEQ ID NO: 8;

(c) a deletion of at least one internal amino acid residue in comparison with SEQ ID NO: 3, SEQ ID NO: 12 or SEQ ID NO: 8; or

(d) one or more substitution in the amino acid sequence in comparison with SEQ ID NO: 3, SEQ ID NO: 12, SEQ ID NO: 8, or of any one of (a) to (c).

35. The polypeptide construct of claim 34, wherein the amino acid deletion is a deletion of 16 amino acids of SEQ ID NO: 3.

36. The polypeptide construct of any one of claims 1 to 35, wherein the second linker comprises or consists of an amino acid sequence having:

(a) a deletion of at least one N-terminal amino acid residue in comparison with SEQ ID NO: 9 or SEQ ID NO: 11;

(b) a deletion of at least one C-terminal amino acid residue in comparison with SEQ ID NO: 9 or SEQ ID NO: 11;

(c) a deletion of at least one internal amino acid residue in comparison with SEQ ID NO: 9 or SEQ ID NO: 11; or

(d) one or more substitution in the amino acid sequence in comparison with SEQ ID NO: 4, 9 or 11, or of any one of (a) to (c).

37. The polypeptide construct of any one of claims 1 to 36, wherein the N-terminal region comprises or consists of an IDR linker, an IDR linker variant, a hybrid linker, a hybrid linker variant, a truncated linker, a truncated linker variant or an elongated linker.

38. The polypeptide construct of any one of claims 1 to 37, wherein the N-terminal region comprises or consists of the amino acid sequence set forth in SEQ ID NO: 3, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

39. The polypeptide construct of any one of claims 1 to 38, wherein one or more of the first TGF β R-LBD and the second TGF β R-LBD comprises or consists of the amino acid sequence set forth in SEQ ID NO: 2, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

40. The polypeptide construct of any one of claims 1 to 39, wherein the first TGF β R-LBD and the second TGF β R-LBD are the same or substantially the same.

41. The polypeptide construct of claim 40, wherein both the first TGF β R-LBD and the second TGF β R-LBD comprise or consist of the amino acid sequence set forth in SEQ ID NO: 2, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

42. The polypeptide construct of any one of claims 1 to 41, wherein the multimerization domain allows dimerization of the polypeptide construct with a second polypeptide construct as defined in any one of claims 1 to 41, in a non-covalent manner.

43. The polypeptide construct of any one of claims 1 to 41, wherein the multimerization domain allows dimerization of the polypeptide construct with a second polypeptide construct as defined in any one of claims 1 to 41, in a covalent manner.

44. The polypeptide construct of any one of claims 1 to 43, wherein the multimerization domain comprises one or more constant region of an antibody.
45. The polypeptide construct of claim 44, wherein the multimerization domain comprises the second constant domain (C_{H2}) and/or the third constant domain (C_{H3}) of an antibody heavy chain.
46. The polypeptide construct of any one of claims 1 to 45, wherein the multimerization domain comprises an Fc region of an antibody heavy chain.
47. The polypeptide construct of any one of claims 44 to 46, wherein the antibody is an IgG antibody.
48. The polypeptide construct of claim 47, wherein the IgG antibody is an IgG1, IgG2, IgG3 or IgG4 antibody, optionally a human antibody.
49. The polypeptide construct of claim 48, wherein the multimerization domain has at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity with a human IgG1, IgG2, IgG3 or IgG4 constant region.
50. The polypeptide construct of any one of claims 1 to 49, wherein the multimerization domain comprises cysteine residues for crosslinking of the polypeptide construct with a second polypeptide construct as defined in any one of claims 1 to 49.
51. The polypeptide construct of claim 50, wherein the multimerization domain comprises at least two cysteine residues for forming a disulfide bridge with the second polypeptide construct.
52. The polypeptide construct of any one of claims 1 to 51, wherein the multimerization domain is engineered to reduce aggregation or to modulate stability of a dimer or multimer of the polypeptide construct.
53. The polypeptide construct of any one of claims 1 to 52, wherein the multimerization domain comprises or consists of the amino acid sequence set forth in SEQ ID NO:49.
54. The polypeptide construct of any one of claims 1 to 52, wherein the multimerization domain comprises or consists of the amino acid sequence set forth in SEQ ID NO:50.
55. The polypeptide construct of any one of claims 1 to 52, wherein the multimerization domain comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOs:

49-80 or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

56. The polypeptide construct of any one of claims 1 to 55, wherein the TGF β -binding region comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOs: 27-48, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

57. The polypeptide construct of any one of claims 1 to 56, wherein the TGF β -binding region comprises or consists of the amino acid sequence set forth in SEQ ID NO: 27.

58. The polypeptide construct of any one of claims 1 to 56, wherein the TGF β -binding region comprises or consists of the amino acid sequence set forth in SEQ ID NO: 29.

59. The polypeptide construct of any one of claims 1 to 56, wherein the TGF β -binding region comprises or consists of the amino acid sequence set forth in SEQ ID NO: 32.

60. The polypeptide construct of any one of claims 1 to 56, wherein the TGF β -binding region comprises or consists of the amino acid sequence set forth in SEQ ID NO: 40.

61. The polypeptide construct of any one of claims 1 to 56, wherein the TGF β -binding region comprises or consists of the amino acid sequence set forth in SEQ ID NO: 41.

62. The polypeptide construct of any one of claims 1 to 61, wherein the polypeptide construct comprises or consists of the amino acid sequence set forth in any one of SEQ ID NOs: 81 to 103 and 105, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

63. The polypeptide construct of any one of claims 1 to 61, wherein the polypeptide construct comprises or consists of the amino acid sequence set forth in SEQ ID NO: 81, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

64. The polypeptide construct of any one of claims 1 to 61, wherein the polypeptide construct comprises or consists of the amino acid sequence set forth in SEQ ID NO: 84, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

65. The polypeptide construct of any one of claims 1 to 61, wherein the polypeptide construct comprises or consists of the amino acid sequence set forth in SEQ ID NO: 87, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.
66. The polypeptide construct of any one of claims 1 to 61, wherein the polypeptide construct comprises or consists of the amino acid sequence set forth in SEQ ID NO: 95, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.
67. The polypeptide construct of any one of claims 1 to 61, wherein the polypeptide construct comprises or consists of the amino acid sequence set forth in SEQ ID NO: 96, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.
68. The polypeptide construct of any one of claims 1 to 67, wherein the polypeptide construct further comprises an amino acid sequence suitable for expression, detection and/or purification of the TGF β binding agent.
69. The polypeptide construct of claim 68, wherein the polypeptide construct further comprises a signal peptide having the sequence set forth in SEQ ID NO: 104, or a sequence substantially identical thereto.
70. The polypeptide construct of any one of claims 1 to 69, wherein the polypeptide construct is a dimeric polypeptide comprising a first and a second polypeptide construct as defined in any one of claims 1 to 69 linked between respective multimerization domains by at least one disulfide bridge.
71. The polypeptide construct of claim 70, wherein the first and the second polypeptide construct comprise the same or substantially the same amino acid sequence.
72. The polypeptide construct of claim 70, wherein the first and the second polypeptide construct comprise different amino acid sequences.
73. The polypeptide construct of claim 72, wherein the first and the second polypeptide construct comprise the same or substantially the same multimerization domains, and different TGF β -binding regions.

74. The polypeptide construct of any one of claims 70 to 73, wherein the first polypeptide and/or the second polypeptide construct further comprises a site for conjugation.
75. The polypeptide construct of claim 74, wherein the first polypeptide and/or the second polypeptide construct is conjugated with a targeting agent, a therapeutic moiety, a detectable moiety, or a diagnostic moiety.
76. The polypeptide construct of claim 75, wherein the targeting agent, the therapeutic moiety, the detectable moiety, or the diagnostic moiety comprises an antibody or antigen binding fragment thereof, a binding agent having affinity for another member of the TGF β family or for another therapeutic target, a radiotherapy agent, an imaging agent, a fluorescent moiety, a cytotoxic agent, an anti-mitotic drug, a nanoparticle-based carrier, a polymer-conjugated drug, a nanocarrier, an imaging agent, a stabilizing agent, a drug, a nanocarrier, or a dendrimer.
77. A polypeptide construct comprising from N-terminus to C-terminus: (i) an amino acid sequence consisting of the amino acid sequence of SEQ ID NO:40; and (ii) an Fc region of human IgG1.
78. A nucleic acid molecule encoding the polypeptide construct of any one of claims 1 to 77.
79. The nucleic acid molecule of claim 78, wherein the nucleic acid molecule encodes the polypeptide construct in a form that is secretable by a selected expression host.
80. A nucleic acid molecule encoding at least one polypeptide having the amino acid sequence set forth in any one of SEQ ID NOs: 81 to 103 and 105, or a sequence substantially identical thereto.
81. A nucleic acid molecule having the sequence set forth in any one of SEQ ID NOs: 106-109, or a sequence substantially identical thereto.
82. The nucleic acid molecule of claim 80, further comprising, at the 5' end, the sequence set forth in SEQ ID NO: 110 or SEQ ID NO: 111, or a sequence substantially identical thereto.
83. A vector comprising the nucleic acid molecule of any one of claims 78 to 82.
84. A cellular host comprising the nucleic acid molecule of any one of claims 78 to 82 or the vector of claim 83.
85. A TGF β binding agent comprising:

a first polypeptide construct as defined in any one of claims 1 to 77, and
a second polypeptide construct as defined in any one of claims 1 to 77;
wherein the first polypeptide construct and the second polypeptide construct are
associated together through their respective multimerization domains
wherein the inhibitory potency of the TGF β binding agent for both TGF β 1 isoform
activity and TGF β 3 isoform activity is greater than for TGF β 2 isoform activity; and
wherein the first linker and the second linker are selected so that the relative inhibitory
potency of the TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform
activity (IC₅₀ ratio for TGF β 3:TGF β 1) is about 2.5:1 or less.

86. The TGF β binding agent of claim 85, wherein the relative inhibitory potency of the
TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio
for TGF β 3:TGF β 1) is: less than about 2.5:1, about 2.3:1 or less, about 2:1 or less, about 1.8:1 or
less, about 1.5:1 or less, about 1.3:1 or less, about 1:1 or less, about 1:1 or less, about 0.8:1 or
less, or about 0.5:1 or less.

87. The TGF β binding agent of claim 85 or 86, wherein the relative inhibitory potency of the
TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio
for TGF β 3:TGF β 1) is from about 1:1 to about 2:1.

88. The TGF β binding agent of claim 87, wherein the relative inhibitory potency of the
TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio
for TGF β 3:TGF β 1) is about 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, or 1.9:1.

89. The TGF β binding agent of claim 88, wherein the relative inhibitory potency of the
TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio
for TGF β 3:TGF β 1) is from about 1.4:1 to about 1.6:1.

90. The TGF β binding agent of claim 89, wherein the relative inhibitory potency of the
TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC₅₀ ratio
for TGF β 3:TGF β 1) is about 1.4:1, about 1.5:1, or about 1.6:1.

91. The TGF β binding agent of any one of claims 85 to 90, wherein the TGF β binding agent
inhibits both TGF β 1 isoform activity and TGF β 3 isoform activity with at least 20-fold, 100-fold,

200-fold, 300-fold, 400-fold, 500-fold, 600-fold, 700-fold, 800-fold, or 900-fold greater potency than TGF β 2 isoform activity.

92. The TGF β binding agent of any one of claims 85 to 91, wherein the TGF β binding agent is a dimer wherein the first polypeptide construct and the second polypeptide construct are linked between their respective multimerization domains by at least one disulfide bridge.

93. The TGF β binding agent of claim 92, wherein the TGF β binding agent is a homodimer, the first polypeptide construct and the second polypeptide construct being the same or substantially the same.

94. The TGF β binding agent of claim 93, wherein the first polypeptide construct and the second polypeptide construct comprise or consist of the sequence set forth in any one of SEQ ID NOs: 81, 84, 87, or 96, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

95. The TGF β binding agent of claim 93 or 94, wherein the first polypeptide construct and the second polypeptide construct comprise or consist of the sequence set forth in SEQ ID NO:87.

96. The TGF β binding agent of claim 93 or 94, wherein the first polypeptide construct and the second polypeptide construct comprise or consist of the sequence set forth in SEQ ID NO:96.

97. The TGF β binding agent of claim 93, wherein the first polypeptide construct and the second polypeptide construct comprises or consists of the sequence set forth in SEQ ID NO:95, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

98. The TGF β binding agent of claim 97, wherein the first polypeptide construct and the second polypeptide construct comprise or consist of the sequence set forth in SEQ ID NO:95.

99. The TGF β binding agent of claim 92, wherein the TGF β binding agent is a heterodimer, the first polypeptide construct and the second polypeptide construct comprising different amino acid sequences.

100. The TGF β binding agent of claim 99, wherein the first polypeptide construct and the second polypeptide construct comprising the same or substantially the same multimerization domains, and different TGF β -binding regions.

101. The TGF β binding agent of claim 100, wherein the different TGF β -binding regions comprise or consist of the amino acid sequence set forth in any one of SEQ ID NOs: 27, 29, 87 and 96, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

102. The TGF β binding agent of claim 100, wherein the different TGF β -binding regions comprise or consist of the amino acid sequence set forth in SEQ ID NO:95, or a sequence at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

103. A TGF β binding agent comprising:

a first polypeptide construct comprising from N-terminus to C-terminus: (i) an amino acid sequence consisting of the amino acid sequence of SEQ ID NO:40; and (ii) a first Fc region of human IgG1, and

a second polypeptide construct comprising from N-terminus to C-terminus: (i) an amino acid sequence consisting of the amino acid sequence of SEQ ID NO:40; and (ii) a second Fc region of human IgG1;

wherein the first polypeptide construct and the second polypeptide construct are linked together through the first and second Fc region of human IgG1.

104. The TGF β binding agent of claim 103, wherein the inhibitory potency of the TGF β binding agent for both TGF β 1 isoform activity and TGF β 3 isoform activity is greater than for TGF β 2 isoform activity; and the relative inhibitory potency of the TGF β binding agent for TGF β 3 isoform activity compared to TGF β 1 isoform activity (IC_{50} ratio for TGF β 3 TGF β 1) is about 2.5:1 or less.

105. A TGF β binding agent, wherein the TGF β binding agent is a homodimer of the polypeptide construct of any one of claims 1 to 77.

106. A pharmaceutical composition comprising the polypeptide construct of any one of claims 1 to 77 or the TGF β binding agent of any one of claims 85 to 105 and a pharmaceutically acceptable carrier, diluent or excipient.

107. The pharmaceutical composition of claim 106, wherein the composition comprises the polypeptide construct of claim 64 or 67 or the TGF β binding agent of claim 95 or 96, or a combination thereof.
108. The pharmaceutical composition of claim 106, wherein the composition comprises the polypeptide construct of claim 66 or the TGF β binding agent of claim 98, or a combination thereof.
109. The pharmaceutical composition of claim 106, wherein the composition comprises the polypeptide construct of claim 66 or the TGF β binding agent of claim 103, or a combination thereof.
110. The pharmaceutical composition of any one of claims 106 to 109, wherein the composition is formulated for administration by injection or infusion.
111. The pharmaceutical composition of claim 110, wherein the composition is formulated for intravenous, subcutaneous, intraperitoneal, or intramuscular administration.
112. A method of manufacturing the polypeptide construct of any one of claims 1 to 77 or the TGF β binding agent of any one of claims 85 to 105, the method comprising expressing the first polypeptide construct and/or the second polypeptide construct in a cell.
113. The method of claim 112, further comprising culturing the cell and isolating and/or purifying the polypeptide construct or the TGF β binding agent expressed in the cell.
114. The method of claim 113, wherein the polypeptide construct and/or the TGF β binding agent is secreted by the cell, and the polypeptide construct and/or the TGF β binding agent is obtained from medium in which the cell is cultured.
115. A method of treating or preventing a TGF β -associated disease or condition in a subject in need thereof, the method comprising administering the polypeptide construct of any one of claims 1 to 77 or the TGF β binding agent of any one of claims 85 to 105 to the subject, such that the TGF β -associated disease or condition is treated or prevented in the subject.
116. The method of claim 115, wherein the subject is a mammal.
117. The method of claim 116, wherein the mammal is a human.

118. The method of any one of claims 115 to 117, wherein the subject has, or is suspected of having, a disease or condition mediated by TGF β 1 and/or TGF β 3.
119. The method of any one of claims 115 to 118, wherein the subject has, or is suspected of having, a disease or condition mediated by TGF β 3.
120. A method of treating or preventing a disease or condition mediated by TGF β 1 and/or TGF β 3 in a subject, the method comprising administering the polypeptide construct of any one of claims 1 to 77 or the TGF β binding agent of any one of claims 85 to 105 to the subject, such that the disease or condition mediated by TGF β 1 and/or TGF β 3 is treated or prevented in the subject.
121. The method of claim 120, wherein the disease is mediated by TGF β 3.
122. The method of any one of claims 115 to 121, wherein the disease or condition is characterized by overexpression or overactivation of TGF β 1 and/or TGF β 3.
123. The method of any one of claims 115 to 122, wherein the disease or condition is fibrosis.
124. The method of claim 123, wherein the fibrosis is pulmonary fibrosis, idiopathic pulmonary fibrosis, renal fibrosis, liver fibrosis, lung fibrosis, kidney fibrosis, bone marrow fibrosis, systemic sclerosis, skin fibrosis, heart fibrosis, myelofibrosis, a fibroproliferative disorder or a connective tissue disorder.
125. The method of any one of claims 115 to 122, wherein the disease or condition is a bone marrow failure disease.
126. The method of claim 125, wherein the disease or condition is Shwachman-Bodian-Diamond syndrome or Fanconi anemia.
127. A method of manufacturing of the polypeptide construct of any one of claims 1 to 77 or the TGF β binding agent of any one of claims 85 to 105, comprising culturing the host cell of claim 84 under conditions suitable for protein expression; and harvesting the polypeptide construct of any one of claims 1 to 77 or the TGF β binding agent of any one of claims 85 to 105.
128. A polypeptide construct or a TGF β binding agent produced by the method of claim 127.