

CLAIMS

What is claimed is:

1. An ~~isolated~~ anti-transforming growth factor beta 3 (TGF β 3) antibody, ~~wherein the antibody selectively neutralizes TGF β 3, and wherein the antibody comprises~~ comprising
5 a VH/VL pair comprising amino acid sequences (respectively) of SEQ ID NOs: 57/56 (v4). ~~one or more of the following features:~~
- ~~(n) the anti-TGF β 3 antibody comprises: (i) heavy chain CDRs comprising CDR H1, H2 and H3, wherein CDR H1 has the amino acid sequence of SEQ ID NO: 4, CDR H2 has the amino acid sequence of one of SEQ ID NOs: 5, 34, 35, and 159, and CDR H3 has the~~
10 ~~amino acid sequence of SEQ ID NO: 6; and (ii) light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 7; CDR L2 has the amino acid sequence of SEQ ID NO: 8, and CDR L3 has the amino acid sequence of SEQ ID NO: 9;~~
- 15 2. The anti-TGF β 3 antibody of claim 1, wherein the antibody selectively neutralizes TGF β 3.
3. The anti-TGF β 3 antibody of any of claim 1 to claim 2, wherein the antibody comprises one or more of the following features:
- (a) the anti-TGF β 3 antibody specifically binds to the beta6/beta7 hairpin region of
20 TGF β 3;
- (b) binding of the anti-TGF β 3 antibody sterically blocks the ability of TGFBR2, but not TGFBR1, to bind TGF β 3;
- (c) binding of the anti-TGF β 3 antibody to TGF β 3 blocks TGFBR2 binding and inhibits the TGFBR1/TGFBR2 signaling receptors from binding to TGF β 3;
- 25 (d) the anti-TGF β 3 antibody directly contacts amino acid residue R394 in the beta6/beta7 hairpin region of human TGF β 3;

(e) the anti-TGFβ3 antibody directly contacts amino acid residue R394 in the beta6/beta7 hairpin region of human TGFβ3 and residue R394 of TGFβ3 makes an ionic salt bridge with the anti-TGFβ3 antibody in the heavy chain CDR2;

5 (f) isoform selectivity of the anti-TGFβ3 antibody for TGFβ3 over TGFβ1 is achieved by direct contact by the antigen binding domain of the anti-TGFβ3 antibody with amino acid residues T387, L389, and T395 of TGFβ3 (human TGFβ3 numbering);

(g) the isoform selectivity of the anti-TGFβ3 antibody for TGFβ3 over TGFβ2 is achieved by direct contact by the antigen binding domain of the anti-TGFβ3 antibody with amino acid residues R325, R394, and V398 of TGFβ3 (human TGFβ3 numbering);

10 ~~(h) the anti-TGFβ3 antibody has reduced toxicity relative to the pan-TGFβ antibody 1D11;~~

~~(i) the anti-TGFβ3 antibody has reduced toxicity in rodents or cynomolgus monkeys relative to the pan-TGFβ antibody 1D11;~~

~~(j) the anti-TGFβ3 antibody has reduced toxicity relative to the pan-TGFβ small molecule inhibitor galunisertib;~~

15 ~~(k) the anti-TGFβ3 antibody has reduced toxicity in rodents relative to the pan-TGFβ small molecule inhibitor galunisertib;~~

~~(l) the anti-TGFβ3 antibody has reduced toxicity relative to the anti-TGFβ1 antibody CAT-192;~~

20 ~~(m) the anti-TGFβ3 antibody has reduced toxicity relative to an isoform selective anti-TGFβ2 antibody and/or anti-TGFβ2/3 antibody;~~

(eh) the anti-TGFβ3 antibody comprises an antigen binding domain that directly contacts amino acid residues R325, K331, W332, H334, E335, T387, I388, L389, Y391, V392, G393, R394, P396, K397, and V398 on human TGFβ3; and

25 (pi) the anti-TGFβ3 antibody as in (eh), wherein the antigen binding domain is within 15-8, 8, 8-5, 7-5, 6-5, or 5 angstroms of the TGFβ3 amino acid residues.

~~2. An isolated anti-TGFβ3 antibody, wherein the antibody comprises: (i) heavy chain CDRs comprising CDR-H1, H2 and H3, wherein CDR-H1 has the amino acid sequence of SEQ ID NO: 4, CDR-H2 has the amino acid sequence of one of SEQ ID NOs: 5, 34,~~

35, and 159, and CDR H3 has the amino acid sequence of SEQ ID NO: 6; and (ii) light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 7; CDR L2 has the amino acid sequence of SEQ ID NO: 8, and CDR L3 has the amino acid sequence of SEQ ID NO: 9.

5 ~~3. The anti-TGFβ3 antibody of claim 1 or claim 2, wherein the antibody comprises a heavy chain variable region (VH) amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 37, 42-53, 55 and 57.~~

10 ~~4. The anti-TGFβ3 antibody of any of claim 1 to claim 3, wherein the antibody comprises a VH amino acid sequence selected from the group consisting of SEQ ID NOs: 23, 37, 42-53, 55 and 57.~~

15 ~~54. The anti-TGFβ3 antibody of any of claim 1 to claim 43, wherein the antibody comprises a complete heavy (H) chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 59, 64, 65-75, 77, and 79.~~

~~65. The anti-TGFβ3 antibody of any of claim 1 to claim 54, wherein the antibody comprises a complete heavy (H) chain amino acid sequence selected from the group consisting of SEQ ID NOs: 29, 59, 64, 65-75, 77 and 79.~~

20 ~~7. The anti-TGFβ3 antibody of any of claim 1 to claim 6, wherein the antibody comprises a light chain variable region (VL) amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity an amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 36, 38-41, 54, and 56.~~

25 ~~8. The anti-TGFβ3 antibody of any of claim 1 to claim 7, wherein the antibody comprises a VL amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 36, 38-41, 54, and 56.~~

30 ~~96. The anti-TGFβ3 antibody of any of claim 1 to claim 85, wherein the antibody comprises a complete light (L) chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 58, 60-63, 76, and 78.~~

~~107.~~ The anti-TGFβ3 antibody of any of claim 1 to claim ~~96~~, wherein the antibody comprises a complete L chain amino acid sequence ~~selected from the group consisting of~~ SEQ ID NOs: ~~28, 58, and 60-63, 76, and 78.~~

~~11. The anti-TGFβ3 antibody of any of claim 1 to claim 10, wherein the antibody~~
5 ~~comprises a VH/VL pair, the VH/VL pair comprising amino acid sequences~~
~~(respectively) selected from the group consisting of SEQ ID NOs: 23/22 (rat 2A10), SEQ~~
~~ID NOs: 37/36 (v1), SEQ ID NOs: 37/38 (v1.1), SEQ ID NOs: 37/39 (v1.2), SEQ ID NOs:~~
~~37/40 (v1.3), SEQ ID NOs: 37/41 (v1.4), SEQ ID NOs: 42/36 (v1.5), SEQ ID NOs: 43/36~~
~~(v1.6), SEQ ID NOs: 44/36 (v1.7), SEQ ID NOs: 45/36 (v2), SEQ ID NOs: 45/38 (v2.1),~~
10 ~~SEQ ID NOs: 45/39 (v2.2), SEQ ID NOs: 45/40 (v2.3), SEQ ID NOs: 45/41 (v2.4), SEQ~~
~~ID NOs: 46/36 (v2.5), SEQ ID NOs: 47/36 (v2.6), SEQ ID NOs: 48/36 (v2.7), SEQ ID~~
~~NOs: 49/36 (v2.8), SEQ ID NOs: 50/36 (v2.9), SEQ ID NOs: 51/36 (h2A10.v2.N54S),~~
~~SEQ ID NOs: 52/36 (h2A10.v2.N54Q), SEQ ID NOs: 53/36 (h2A10.v2.T56A), SEQ ID~~
~~NOs: 55/54 (v3), and SEQ ID NOs: 57/56 (v4).~~

15 ~~128.~~ The anti-TGFβ3 antibody of any of claim 1 to claim ~~117~~, wherein the antibody

~~comprises a complete H/L chain pair, the complete H/L chain pair comprising amino acid~~
~~sequences (respectively) selected from the group consisting of SEQ ID NOs: 29/28 (rat~~
~~2A10), SEQ ID NOs: 59/58 (v1), SEQ ID NOs: 59/60 (v1.1), SEQ ID NOs: 59/61 (v1.2),~~
~~SEQ ID NOs: 59/62 (v1.3), SEQ ID NOs: 59/63 (v1.4), SEQ ID NOs: 64/58 (v1.5), SEQ~~
20 ~~ID NOs: 65/58 (v1.6), SEQ ID NOs: 66/58 (v1.7), SEQ ID NOs: 67/58 (v2), SEQ ID NOs:~~
~~67/60 (v2.1), SEQ ID NOs: 67/61 (v2.2), SEQ ID NOs: 67/62 (v2.3), SEQ ID NOs: 67/63~~
~~(v2.4), SEQ ID NOs: 68/58 (v2.5), SEQ ID NOs: 69/58 (v2.6), SEQ ID NOs: 70/58 (v2.7),~~
~~SEQ ID NOs: 71/58 (v2.8), SEQ ID NOs: 72/58 (v2.9), SEQ ID NOs: 73/58~~
~~(h2A10.v2.N54S), SEQ ID NOs: 74/58 (h2A10.v2.N54Q), SEQ ID NOs: 75/58~~
25 ~~(h2A10.v2.T56A), SEQ ID NOs: 77/76 (v3), and of SEQ ID NOs: 79/78 (v4).~~

~~13. The anti-TGFβ3 antibody of any of claim 1 to claim 10, wherein the antibody~~
~~comprises a VL of SEQ ID NO: 22 comprising one or more framework modifications~~
~~selected from the group consisting of: 4L or 4M, 38H or 38Q, 43A or 43Q, and 58V.~~

~~14. The anti-TGFβ3 antibody of any of claim 1 to claim 10, wherein the VL comprises a~~
30 ~~set of framework modifications selected from the group consisting of:~~
~~(i) 4L in FR1, 38H and 43Q in FR2, 58I in FR3 (h2A10.v1 and h2A10.v2);~~
~~(ii) 4M in FR1 (h2A10.v1.1 and h2A10.v2.1);~~

- (iii) 38Q in FR2 (h2A10.v1.2 and h2A10.v2.2);
 (iv) 43A in FR2 (h2A10.v1.3 and h2A10.v2.3);
 (v) 58V in FR3 (h2A10.v1.4 and h2A10.v2.4);
 (vi) 38Q, 43A in FR2, 58V in FR3 (h2A10.v3 and h2A10.v4);
 5 (vii) 58V in FR3 (h2A10.v1.4 and h2A10.v2.4); and
 (vi) 38Q, 43A in FR2, 58V in FR3 (h2A10.v3 and h2A10.v4).
15. ~~The anti-TGFβ3 antibody of any of claim 1 to claim 10, claim 13 and claim 14, wherein the antibody comprises a VH of SEQ ID NO: 23 comprising one or more framework modifications selected from the group consisting of: 47L or 47W; 49A, 49S, or~~
 10 ~~49G; 73D or 73N; and 76N, 78D or 78L, 78A, or 78V.~~
16. ~~The anti-TGFβ3 antibody of claim 15, wherein the VH comprises a set of framework modifications selected from the group consisting of:-~~
 (i) ~~47L, 49A in FR2, 78V in FR3 (h2A10.v1);~~
 (ii) ~~47L, 49A in FR2, 73D, 76S, 78V in FR3 (h2A10.v2);~~
 15 (iii) ~~47W in FR2 (h2A10.v1.5);~~
 (iv) ~~49G in FR2 (h2A10.v1.6);~~
 (v) ~~78A in FR3 (h2A10.v1.7);~~
 (vi) ~~47W in FR2 (h2A10.v2.5);~~
 (vii) ~~49S in FR2 (h2A10.v2.6);~~
 20 (viii) ~~73N in FR3 (h2A10.v2.7);~~
 (ix) ~~76N in FR3 (h2A10.v2.8);~~
 (x) ~~78L in FR3 (h2A10.v2.9); and~~
 (xi) ~~49S in FR2, 76N, 78L in FR3 (h2A10.v3 and h2A10.v4).~~
17. ~~The antibody of claim 13 or claim 15 comprising a VL, wherein the VL retains leucine~~
 25 ~~(L) at position 4 in framework I and leucine (L) at position 47 in framework II.~~
18. ~~The antibody of claim 15 or claim 17, wherein the VH retains D at position 73 in framework III of VH from r2A10.~~
19. ~~The anti-TGFβ3 antibody of any one of claim 1 to claim 12, wherein the antibody comprises a CDR H2 having the amino acid sequence of SEQ ID NO: 5.~~

- ~~20. The anti-TGF β 3 antibody of any one of claim 1 to claim 12, wherein the anti-TGF β 3 antibody comprises a CDR-H2 having the amino acid sequence of SEQ ID NO: 159.~~
- ~~21. The anti-TGF β 3 antibody of claim 20, wherein the antibody comprises a VH amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 52.~~
- ~~22. The anti-TGF β 3 antibody of claim 20 or claim 21, wherein the antibody comprises the VH amino acid sequence of SEQ ID NO: 52.~~
- ~~23. The anti-TGF β 3 antibody of any of claim 20 to claim 22, wherein the antibody comprises a complete H chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 74.~~
- ~~24. The anti-TGF β 3 antibody of any of claim 20 to claim 23, wherein the antibody comprises the complete H chain amino acid sequence of SEQ ID NO: 74.~~
- ~~25. The anti-TGF β 3 antibody of any of claim 20 to claim 24, wherein the antibody comprises a VL amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 36, and 38-41.~~
- ~~26. The anti-TGF β 3 antibody of any of claim 20 to claim 25, wherein the antibody comprises a VL amino acid sequence selected from the group consisting of SEQ ID NOs: 22, 36, and 38-41.~~
- ~~27. The anti-TGF β 3 antibody of any of claim 20 to claim 26, wherein the antibody comprises a complete L chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 58, and 60-63.~~
- ~~28. The anti-TGF β 3 antibody of any of claim 20 to claim 27, wherein the antibody comprises a complete L chain amino acid sequence selected from the group consisting of SEQ ID NOs: 28, 58, and 60-63.~~
- ~~29. The anti-TGF β 3 antibody of claim 20, wherein the antibody comprises a VH/VL pair comprising the amino acid sequences (respectively) of SEQ ID NOs: 52/36.~~

- ~~30. The anti TGFβ3 antibody of claim 20, wherein the antibody comprises a complete H/L chain pair, the H/L chain pair comprising the amino acid sequences (respectively) of SEQ ID NOs: 74/58.~~
- 5 ~~31. The anti TGFβ3 antibody of any one of claim 1 to claim 12, wherein the antibody comprises a CDR H2 having the amino acid sequence of SEQ ID NO: 34.~~
- ~~32. The anti TGFβ3 antibody of claim 31, wherein the antibody comprises a VH amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 55.~~
- 10 ~~33. The anti TGFβ3 antibody of claim 31 or claim 32, wherein the antibody comprises the VH amino acid sequence of SEQ ID NO: 55.~~
- ~~34. The anti TGFβ3 antibody of any of claim 31 to claim 33, wherein the antibody comprises a complete H chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 77.~~
- 15 ~~35. The anti TGFβ3 antibody of any of claim 31 to claim 34, wherein the antibody comprises the complete H chain amino acid sequence of SEQ ID NO: 77.~~
- ~~36. The anti TGFβ3 antibody of any of claim 31 to claim 35, wherein the antibody comprises a VL amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID~~
- 20 ~~NO: 54.~~
- ~~37. The anti TGFβ3 antibody of any of claim 31 to claim 36, wherein the antibody comprises the VL amino acid sequence of SEQ ID NO: 54.~~
- ~~38. The anti TGFβ3 antibody of any of claim 31 to claim 37, wherein the antibody comprises a complete L chain amino acid sequence having at least 95%, at least~~
- 25 ~~96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 76.~~
- ~~39. The anti TGFβ3 antibody of any one of claim 31 to claim 38, wherein the antibody comprises the complete L chain amino acid sequence of SEQ ID NO: 76.~~

40. ~~The anti TGFβ3 antibody of claim 31, wherein the antibody comprises a VH/VL pair, the VH/VL pair comprising the amino acid sequences (respectively) of SEQ ID NOs: 55/54.~~
- 5 41. ~~The anti TGFβ3 antibody of claim 31, wherein the antibody comprises a complete H/L chain pair, the H/L chain pair comprising the amino acid sequences (respectively) of SEQ ID NOs: 77/76.~~
42. ~~The anti TGFβ3 antibody of any one of claim 1 to claim 12, wherein the antibody comprises a CDR H2 having the amino acid sequence of SEQ ID NO: 35.~~
- 10 43. ~~The anti TGFβ3 antibody of claim 42, wherein the antibody comprises a VH amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 57.~~
44. ~~The anti TGFβ3 antibody of claim 42 or claim 43, wherein the antibody comprises the VH amino acid sequence of SEQ ID NO: 57.~~
- 15 45. ~~The anti TGFβ3 antibody of any of claim 42 to claim 44, wherein the antibody comprises a complete H chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 79.~~
46. ~~The anti TGFβ3 antibody of any of claim 42 to claim 45, wherein the antibody comprises a complete H chain amino acid sequence of SEQ ID NO: 79.~~
- 20 47. ~~The anti TGFβ3 antibody of any of claim 42 to claim 46, wherein the antibody comprises a VL amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 56.~~
- 25 48. ~~The anti TGFβ3 antibody of any one of claim 42 to claim 47, wherein the antibody comprises the VL amino acid sequence of SEQ ID NO: 56.~~
49. ~~The anti TGFβ3 antibody of any of claim 42 to claim 48, wherein the antibody comprises a complete L chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 76~~

~~50. The anti-TGF β 3 antibody of any of claim 42 to claim 49, wherein the antibody comprises the complete L chain amino acid sequence of SEQ ID NOs: 76.~~

~~51. The anti-TGF β 3 antibody of claim 42, wherein the antibody comprises a VH/VL pair comprising the amino acid sequences (respectively) of SEQ ID NOs: 57/56.~~

5 ~~52. The anti-TGF β 3 antibody of claim 42, wherein the antibody comprises a complete H/L chain pair, the H/L chain pair comprising the amino acid sequences (respectively) of SEQ ID NOs: 79/78.~~

~~53. An anti-TGF β 3 antibody comprising:~~

10 ~~(a) (i) heavy chain CDRs comprising CDR H1, H2 and H3, wherein CDR H1 has the amino acid sequence of SEQ ID NO: 4, CDR H2 has the amino acid sequence of one of SEQ ID NO: 35, and CDR H3 has the amino acid sequence of SEQ ID NO: 6; and (ii) light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 7; CDR L2 has the amino acid sequence of SEQ ID NO: 8, and CDR L3 has the amino acid sequence of SEQ ID NO: 9;~~

15 ~~(b) a VH/VL pair, the VH of the VH/VL pair comprising the amino acid sequence of SEQ ID NO: 57, and the VL of the VH/VL pair comprising the amino acid sequence of SEQ ID NO: 56; or~~

20 ~~(c) a complete H/L chain pair, the H chain of the H/L chain pair comprising the amino acid sequence of SEQ ID NO: 79 and the L chain of the H/L chain pair comprising the amino acid sequence of SEQ ID NO: 78.~~

~~54. An isolated anti-TGF β 2/3 antibody, wherein the antibody selectively neutralizes TGF β 2 and TGF β 3, and wherein the antibody comprises one or more of the following features:~~

25 ~~(a) selectivity of the anti-TGF β 2/3 antibody for TGF β 2 and TGF β 3 over human TGF β 1, with respect to selective neutralization, is achieved by direct contact of the antibody's antigen binding domain with amino acid residue E373 TGF β 2 or TGF β 3 (human TGF β 2 numbering);~~

~~(b) the anti-TGF β 2/3 antibody neutralizes TGF β 2 and/or TGF β 3 via an allosteric mechanism;~~

30 ~~(c) the anti-TGF β 2/3 antibody induces a conformational change in TGF β 2 and/or TGF β 3 homodimer;~~

~~(d) the anti-TGFβ2/3 antibody induces a conformational change in TGFβ2 and/or TGFβ3 homodimer, wherein the conformational change comprises the two monomers pinching together by several degrees;~~

~~(e) the anti-TGFβ2/3 antibody is a divalent antibody or a monovalent antibody;~~

~~(f) the anti-TGFβ2/3 antibody comprises (i) heavy chain CDRs comprising CDR-H1, H2 and H3, wherein CDR-H1 has the amino acid sequence of SEQ ID NO: 10, CDR-H2 has the amino acid sequence of SEQ ID NO: 11, and CDR-H3 has the amino acid sequence of SEQ ID NO: 12; and (ii) light chain CDRs comprising CDR-L1, L2 and L3, wherein CDR-L1 has the amino acid sequence of SEQ ID NO: 13; CDR-L2 has the amino acid sequence of SEQ ID NO: 14, and CDR-L3 has the amino acid sequence of SEQ ID NO: 15;~~

~~(g) the anti-TGFβ2/3 antibody specifically binds to TGFβ2 homodimer, the TGFβ2 homodimer having a first and a second TGFβ2 monomer, and wherein the anti-TGFβ2/3 antibody comprises an antigen-binding domain that directly contacts (i) amino acid residues V313, Q314, D315, R320, L322, Y323, R328, D329, F345, and A347 of the first TGFβ2 monomer, and (ii) amino acid residues N368, T369, I370, N371, P372, E373, A374, S375, A376, and S377 of the second TGFβ2 monomer (human TGFβ2 numbering);~~

~~(h) the anti-TGFβ2/3 antibody as in (g), wherein the antigen-binding domain is within 5 angstroms of the TGFβ2 and/or TGFβ3 amino acid residues;~~

~~(i) wherein the anti-TGFβ2/3 antibody specifically binds to the same epitope on TGFβ3 as in (g); and~~

~~(j) the anti-TGFβ2/3 antibody does not neutralize TGFβ2 and/or TGFβ3 in monovalent form.~~

~~55. The anti-TGFβ2/3 antibody of claim 54, wherein the antibody comprises a VH amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 81, 83, 86-88, 93-100, and 102-105.~~

~~56. The anti-TGFβ2/3 antibody of claim 54 or claim 55, wherein the antibody comprises a VH amino acid sequence selected from the group consisting of SEQ ID NOs: 27, 81, 83, 86-88, 93-100, and 102-105.~~

~~57. The anti-TGFβ2/3 antibody of any of claim 54 to claim 56, wherein the antibody comprises a complete H chain amino acid sequence having at least 95%, at least 96%, at~~

~~least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 33, 107, 109, 112-114, and 119-130.~~

58. The anti-TGF β 2/3 antibody of any of claim 54 to claim 57, wherein the antibody comprises a VL amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 80, 82, 84, 85, 89-92, and 101.

59. The anti-TGF β 2/3 antibody of any of claim 54 to claim 56, wherein the antibody comprises a VL amino acid sequence selected from the group consisting of SEQ ID NOs: 26, 80, 82, 84, 85, 89-92, and 101.

60. The anti-TGF β 2/3 antibody of any of claim 54 to claim 59, wherein the antibody comprises a complete L chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 32, 106, 108, 110, 111, 115-118, and 186.

61. The anti-TGF β 2/3 antibody of any of claim 54 to claim 60, wherein the antibody comprises a complete L chain amino acid sequence selected from the group consisting of SEQ ID NOs: 32, 106, 108, 110, 111, 115-118, and 186.

62. The anti-TGF β 2/3 antibody of claim 54, wherein the antibody comprises a VH/VL pair, the VH/VL pair comprising amino acid sequences (respectively) selected from the group consisting of SEQ ID NOs: 27/26 (rabbit 4A11), SEQ ID NOs: 81/80 (v1), SEQ ID NOs: 81/82 (v2), SEQ ID NOs: 83/80 (v3), SEQ ID NOs: 83/82 (v4), SEQ ID NOs: 81/84 (v5), SEQ ID NOs: 81/85 (v6), SEQ ID NOs: 83/84 (v7), SEQ ID NOs: 86/84 (v7.1), , SEQ ID NOs: 87/84 (v7.2), SEQ ID NOs: 88/84 (v7.3), SEQ ID NOs: 83/89 (v7.4), SEQ ID NOs: 83/90 (v7.5), SEQ ID NOs: 83/91 (v7.6), SEQ ID NOs: 83/92 (v7.7), SEQ ID NOs: 93/84 (v7.8), SEQ ID NOs: 94/84 (v7.9), SEQ ID NOs: 95/84 (v7.10), SEQ ID NOs: 96/84 (v7.11), SEQ ID NOs: 97/84 (v7.12), SEQ ID NOs: 98/84 (v7.13), SEQ ID NOs: 99/84 (v7.14), SEQ ID NOs: 100/84 (v7.15), SEQ ID NOs: 102/101 (v7.16), SEQ ID NOs: 103/101 (v7.17), SEQ ID NOs: 104/101 (v7.18), SEQ ID NOs: 105/101 (v7.19), and SEQ ID NOs: 83/85 (v8).

63. ~~The anti TGFβ2/3 antibody of claim 54, wherein the antibody comprises a complete H/L chain pair, the complete H/L chain pair comprising amino acid sequences (respectively) selected from the group consisting of SEQ ID NOs: 32/33 (rabbit 4A11), SEQ ID NOs: 107/106 (v1), SEQ ID NOs: 107/108 (v2), SEQ ID NOs: 109/106 (v3), SEQ ID NOs: 109/108 (v4), SEQ ID NOs: 107/110 (v5), SEQ ID NOs: 107/111 (v6), SEQ ID NOs: 109/110 (v7), SEQ ID NOs: 112/110 (v7.1), SEQ ID NOs: 113/110 (v7.2), SEQ ID NOs: 114/110 (v7.3), SEQ ID NOs: 114/115 (v7.4), SEQ ID NOs: 114/116 (v7.5), SEQ ID NOs: 114/117 (v7.6), SEQ ID NOs: 114/118 (v7.7), SEQ ID NOs: 119/110 (v7.8), SEQ ID NOs: 120/110 (v7.9), SEQ ID NOs: 121/110 (v7.10), SEQ ID NOs: 122/110 (v7.11), SEQ ID NOs: 123/110 (v7.12), SEQ ID NOs: 124/110 (v7.13), SEQ ID NOs: 125/110 (v7.14), SEQ ID NOs: 126/110 (v7.15), SEQ ID NOs: 127/186 (v7.16), SEQ ID NOs: 128/186 (v7.17), SEQ ID NOs: 129/186 (v7.18), SEQ ID NOs: 130/186 (v7.19), and SEQ ID NOs: 114/111 (v8).~~
64. ~~The anti TGFβ2/3 antibody of claim 54, wherein the antibody comprises a VL comprising the amino acid sequence of SEQ ID NO: 26 comprising one or more framework modifications selected from the group consisting of: 2A or 2I, 4L, 36F or 36Y, 43P or 43A, and 58V or 58I.~~
65. ~~The anti TGFβ2/3 antibody of claim 54, wherein the VL comprises a set of framework modifications selected from the group consisting of:-~~
- (i) 2A and 4L in FR1 and 36F in FR2 (h4A11.v1 and h4A11.v3);
 - (ii) 2A and 4L in FR1 and 36F and 43P in FR2 (h4A11.v2 and h4A11.v4);
 - (iii) 2A in FR1, 36F and 43P in FR2 and 58V in FR3 (h4A11.v5 and h4A11.v7);
 - (iv) 2A and 4L in FR1 and 36F in FR2 (h4A11.v6 and h4A11.v8);
 - (v) 2I in FR1 (h4A11.v7.4);
 - (vi) 36Y in FR2 (h4A11.v7.5);
 - (vii) 43A in FR2 (h4A11.v7.6);
 - (viii) 58I in FR3 (h4A11.v7.7); and
 - (ix) 2I in FR1, 43A in FR2, 58I in FR3 (h4A11.v7.16-19).
66. ~~The anti TGFβ2/3 antibody of claim 54, wherein the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 27 comprising one or more framework modifications selected from the group consisting of: deletion of 1E, 2Q or 2V,~~

~~24V, 37V or 37I, 48I, 49G, 67F or 67V, 71K or 71V, 73S or 73T, deletion of 75K and 76N, 78V or 78F, 91F or 91Y, 105P or 105Q.~~

~~67. The anti-TGF β 2/3 antibody of claim 54 or claim 66, wherein the VL comprises a set of framework modifications selected from the group consisting of:-~~

- ~~(i) 2Q and 24V in FR1, 48I and 49G in FR2, 71K, 73S, 78V and 91F in FR3 and 105P in FR4 (h4A11.v1, h4A11.v2, h4A11.v5, h4A11.v6);~~
- ~~(ii) 2Q in FR1, 37V in FR2, 67F, 71K, 73S, 78V and 91F in FR3 and 105P in FR4 (h4A11.v3, h4A11.v4, h4A11.v7, h4A11.v8);~~
- ~~(iii) delete 1E in FR1 (h4A11.v7.1);~~
- ~~(iv) delete 75K and 76N in FR3 (h4A11.v7.2);~~
- ~~(v) delete 1E in FR1 and 75K76N in FR3 (h4A11.v7.3);~~
- ~~(vi) 2V in FR1 (h4A11.v7.8);~~
- ~~(vi) 37I in FR2 (h4A11.v7.9);~~
- ~~(vii) 67V in FR3 (h4A11.v7.10);~~
- ~~(viii) 71V in FR3 (h4A11.v7.11);~~
- ~~(ix) 73T in FR3 (h4A11.v7.12);~~
- ~~(x) 78F in FR3 (h4A11.v7.13);~~
- ~~(xi) 91Y in FR3 (h4A11.v7.14);~~
- ~~(xii) 105Q in FR4 (h4A11.v7.15);~~
- ~~(xiii) 2V in FR1, 37I in FR2, 67V, 73T, 78F in FR3, 105Q in FR4 ((h4A11.v7.16);~~
- ~~(xiv) 2V in FR1, 37I in FR2, 67V, 73T, 91Y in FR3, 105Q in FR4 (h4A11.v7.17);~~
- ~~(xv) 2V in FR1, 37I in FR2, 67V, 73T in FR3, 105Q in FR4 (h4A11.v7.18); and~~
- ~~(xvi) 2V in FR1, 37I in FR2, 67V, 73T, deletion of 75K and 76N in FR3, 105Q in FR4 (h4A11.v7.19).-~~

~~68. An isolated anti-TGF β 2 antibody, wherein the antibody comprises:~~

- ~~(a) heavy chain CDRs comprising CDR H1, H2 and H3, wherein CDR H1 has the amino acid sequence of SEQ ID NO: 16, CDR H2 has the amino acid sequence of SEQ ID NO: 17, and CDR H3 has the amino acid sequence of SEQ ID NO: 18; and~~
- ~~(b) light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 19; CDR L2 has the amino acid sequence of SEQ ID NO: 20, and CDR L3 has the amino acid sequence of SEQ ID NO: 21.~~

69. ~~The anti-TGF β 2 antibody of claim 68, wherein the antibody selectively neutralizes TGF β 2.~~
70. ~~The anti-TGF β 2 antibody of claim 69, wherein the antibody:~~
- 5 ~~(a) has reduced toxicity relative to the pan-TGF β antibody 1D11;~~
- ~~(b) has reduced toxicity in rodents relative to the pan-TGF β antibody 1D11;~~
- ~~(c) has reduced toxicity relative to the pan-TGF β small molecule inhibitor galunisertib; and/or~~
- ~~(d) has reduced toxicity in rodents relative to the pan-TGF β small molecule inhibitor galunisertib.~~
- 10 71. ~~The anti-TGF β 2 antibody of claim 68 or claim 69, wherein the antibody comprises a VH amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 132, and 138-142.~~
- 15 72. ~~The anti-TGF β 2 antibody of claim 71, wherein the antibody comprises a VH amino acid sequence selected from the group consisting of SEQ ID NOs: 25, 132, and 138-142.~~
73. ~~The anti-TGF β 2 antibody of claim 68 or claim 69, wherein the antibody comprises a complete H chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 146, and 152-156.~~
- 20 74. ~~The anti-TGF β 2 antibody of claim 73, wherein the antibody comprises a complete H chain amino acid sequence selected from the group consisting of SEQ ID NOs: 31, 146, and 152-156.~~
75. ~~The anti-TGF β 2 antibody of claim 68 or claim 69, wherein the antibody comprises a VL amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to the amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 131, 133-137, 143, and 144.~~
- 25 76. ~~The anti-TGF β 2 antibody of claim 75, wherein the antibody comprises a VL amino acid sequence selected from the group consisting of SEQ ID NOs: 24, 131, 133-137, 143, and 144.~~

77. ~~The anti TGFβ2 antibody of claim 68 or claim 69, wherein the antibody comprises a complete L chain amino acid sequence having at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 30,145, 147-151, 157, and 158.~~
- 5 78. ~~The anti TGFβ2 antibody of claim 77, wherein the antibody comprises a complete L chain amino acid sequence selected from the group consisting of SEQ ID NOs: 30,145, 147-151, 157, and 158.~~
- 10 79. ~~The anti TGFβ2 antibody of claim 68 or claim 69, wherein the antibody comprises a VH/VL pair, the VH/VL pair comprising amino acid sequences selected from the group consisting of SEQ ID NOs: 25/24 (rabbit 6F12), SEQ ID NOs: 132/131 (v1), SEQ ID NOs: 132/133 (v1.1), SEQ ID NOs: 132/134 (v1.2), SEQ ID NOs: 132/135 (v1.3), SEQ ID NOs: 132/136 (v1.4), SEQ ID NOs: 132/137 (v1.5), SEQ ID NOs: 138/131 (v1.6), SEQ ID NOs: 139/131 (v1.7), SEQ ID NOs: 140/131 (v1.8), SEQ ID NOs: 141/131 (v1.9), SEQ ID NOs: 142/131 (v2), SEQ ID NOs: 132/143 (v3), and SEQ ID NOs:~~
- 15 ~~142/144 (v4).~~
- 20 80. ~~The anti TGFβ2 antibody of claim 68 or claim 69, wherein the antibody comprises a complete H/L chain pair, the complete H/L chain pair comprising amino acid sequences selected from the group consisting of SEQ ID NOs: 31/30 (rabbit 6F12), SEQ ID NOs: 146/145 (v1), SEQ ID NOs: 146/147 (v1.1), SEQ ID NOs: 146/148 (v1.2), SEQ ID NOs: 146/149 (v1.3), SEQ ID NOs: 146/150 (v1.4), SEQ ID NOs: 146/151 (v1.5), SEQ ID NOs: 152/145 (v1.6), SEQ ID NOs: 153/145 (v1.7), SEQ ID NOs: 154/145 (v1.8), SEQ ID NOs: 155/145 (v1.9), SEQ ID NOs: 156/145 (v2), SEQ ID NOs: 146/157 (v3), and SEQ ID NOs: 156/158 (v4).~~
- 25 81. ~~The anti TGFβ2 antibody of claim 68 or claim 69, wherein the antibody comprises a VL comprising the amino acid sequence of SEQ ID NO: 24 comprising one or more framework mutations selected from the group consisting of 43S or 43A, 66G, 69T, 71F, and 87Y.~~
- 30 82. ~~The anti TGFβ2 antibody of claim 81, wherein the VL comprises a set of framework mutations selected from the group consisting of:~~
- ~~(i) 43S in FR2 and 66E, 69P, 71Y and 87F in FR3 (h6F12.v1 and h6F12.v2);~~
- ~~(ii) 43S in FR2 and 58V, 66E, 69P, 71Y and 87F in FR3 (h6F12.v3 and h6F12.v4);~~

- (iii) ~~43A in FR2 (h6F12.v1.1);~~
- (iv) ~~66G in FR3 (h6F12.v1.2);~~
- (v) ~~69T in FR3 (h6F12.v1.3);~~
- (vi) ~~71F in FR3 (h6F12.v1.4); and~~
- (vii) ~~87Y in FR3 (h6F12.v1.5);~~

~~83 The anti-TGF β 2 antibody of claim 68 or claim 69, wherein the antibody comprises a VH comprising the amino acid sequence of SEQ ID NO: 25 comprising one or more framework mutations selected from the group consisting of 37V or 37I, 48M or 48L, 49G or 49A, 67L, 71K and 78V, and 105P or 105R.~~

~~84. The anti-TGF β 2 antibody of claim 83, wherein the VH comprises a set of framework mutations selected from the group consisting of:~~

- (i) ~~37V, 48M and 49G in FR2 and 105P in FR4 (h6F12.v1 and h6F12.v3);~~
- (ii) ~~37V and 48M in FR2, 67L, 71K and 78V in FR3 and 105P in FR4 (h6F12.v2 and h6F12.v4);~~

- (iii) ~~37I in FR2 (h6F12.v1.6);~~
- (iv) ~~48L in FR2 (h6F12.v1.7);~~
- (v) ~~49A in FR2 (h6F12.v1.8);~~
- (vi) ~~105R in FR4 (h6F12.v1.9);~~
- (vii) ~~37V, 48M and 49G in FR2 and 105P in FR4 (h6F12.v1 and h6F12.v3);~~
- (viii) ~~37V and 48M in FR2, 67L, 71K and 78V in FR3 and 105P in FR4 (6F12.v2 and h6F12.v4);~~
- (ix) ~~37I in FR2 (h6F12.v1.6);~~
- (x) ~~48L in FR2 (h6F12.v1.7);~~
- (xi) ~~49A in FR2 (h6F12.v1.8); and~~
- (xii) ~~105R in FR4 (h6F12.v1.9).~~

~~85~~2. The anti-TGF β 3 antibody of any one of claim 1 ~~to claim 53~~8, ~~or the anti-TGF β 2/3 antibody of any one of claim 54 claim 66,~~ wherein the antibody specifically binds to human TGF β 3, optionally wherein the antibody specifically binds to both the immature and mature forms of TGF β 3.

~~86. The anti-TGF β 3 antibody of any one of claim 1 claim 53, wherein the antibody specifically binds to both the immature and mature forms of TGF β 3.~~

~~87. The anti-TGF β 2/3 antibody of any one of claim 54—claim 66, or the anti-TGF β 2 antibody of any one of claim 68—claim 81, wherein the antibody specifically binds to human TGF β 2.~~

5 ~~88~~10. ~~An~~The antibody of any one of claim 1 ~~—to~~claim 879, which is a monoclonal antibody.

~~89~~11. ~~An~~The antibody of any one of claim 1 ~~—to~~claim 879, which is a human, humanized, or chimeric antibody.

~~90~~12. ~~An~~The antibody of any one of claim 1 ~~—to~~claim 879, which is an antibody fragment.

10 ~~94~~13. ~~An~~The antibody of any one of claim 1 ~~—to~~claim 879, comprising a human Fc region that is an IgG1 or IgG4 isotype, optionally wherein the antibody comprises a human Fc region that is an IgG1 isotype.

~~92. The antibody of claim 91, comprising a human Fc region that is an IgG1 isotype.~~

15 ~~93~~14. The antibody of claim ~~91 or claim 92~~13, wherein the Fc region comprises a modification to remove the glycosylation site at amino acid residue position N297 (EU numbering as in Kabat), optionally wherein the modification is a mutation selected from N297G or N297A, and optionally wherein the modification is the mutation N297G.

~~94. The antibody of claim 93, wherein the modification is a mutation selected from N297G or N297A.~~

20 ~~95. The antibody of claim 94, wherein the modification is the mutation N297G.~~

~~96~~15. The antibody of any one of claim ~~94—13—~~to claim ~~95~~14, wherein the Fc region is modified to remove effector function.

~~97~~16. ~~An~~The antibody of any one of claim 1 ~~—to~~claim 9615, wherein the antibody has a C_{max} of about 230-260 μ g/ml and/or a half life ($t_{1/2}$) of about 15 to 16 days.

25 ~~98~~17. ~~A Isolated~~ nucleic acid encoding the antibody of any one of claim 1 ~~—to~~claim 9716.

~~99~~18. A host cell comprising the nucleic acid of claim ~~98~~17.

- ~~100~~19. A method of producing an antibody comprising culturing the host cell of claim ~~99~~18, so that the antibody is produced.
- ~~101~~20. The method of claim ~~100~~19, further comprising recovering the antibody from the host cell.
- 5 ~~102~~21. An antibody produced by the method of claim ~~100~~19 or claim ~~101~~20.
- ~~103~~22. An immunoconjugate comprising the antibody of any one of claim 1 to claim 97
16 and a cytotoxic agent.
- ~~104~~23. A pharmaceutical formulation comprising the antibody of any one of claim 1 ~~to~~
claim ~~97~~16, or the immunoconjugate of claim ~~103~~22 and a pharmaceutically acceptable
10 carrier.
- ~~105~~24. ~~A~~ The pharmaceutical formulation ~~comprising the antibody~~ of claim ~~104~~23, further
comprising an additional therapeutic agent, optionally wherein the additional therapeutic
agent is selected from the group consisting of pirfenidone, nintedanib, mycophenylate
mofetil, an IL-6 inhibitor (e.g., tocilizumab), an anti-CTFG antibody (e.g., FG-3019), an
15 autotaxin inhibitor, a JAK inhibitor, an IL-11 inhibitor, and PTX2.
- ~~106. The pharmaceutical formulation of claim 105, wherein the additional therapeutic~~
~~agent is selected from the group consisting of pirfenidone, nintedanib, mycophenylate~~
~~mofetil, an IL-6 inhibitor (e.g., tocilizumab), an anti-CTFG antibody (e.g., FG-3019), an~~
~~autotaxin inhibitor, a JAK inhibitor, an IL-11 inhibitor, and PTX2.~~
- 20 ~~107~~25. The antibody of any one of claim 1 ~~to~~ claim ~~97~~16, for use as a medicament.
- ~~108. The antibody of any one of claim 1 to claim 97, for use in treating a TGFβ-related~~
~~disorder.~~
- ~~109. The antibody of claim 1 and the antibody of claim 68, for use in combination to treat~~
~~a TGFβ-related disorder.~~
- 25 ~~110. The antibodies of claim 108 or claim 109, wherein the TGFβ-related disorder is~~
~~fibrosis.~~
- ~~111. The antibodies of claim 110, wherein the fibrosis is a fibrotic condition of the lung,~~
~~liver, heart, kidney, pancreas, eye, and/or skin.~~

~~112. The antibody of any one of claim 1—claim 97 for use in the manufacture of a medicament for inhibiting TGFBR-dependent SMAD signaling, for inhibiting the assembly of TGF β TGFBR signaling complexes, for inhibiting TGF β signaling through the TGFBR1/R2 complex, for inhibiting TGF β signaling through the TGFBR2/ALK1 complex facilitated by endoglin, and/or for inhibiting new collagen synthesis.~~

~~113~~26. Use of ~~an~~the antibody according to any one of claim 1 ~~to—~~claim ~~97~~16, in the manufacture of a medicament for ~~treating~~the treatment of a TGF β -related disorder in a subject, optionally wherein the TGF β -related disorder is fibrosis, and optionally wherein the fibrosis is scleroderma/systemic sclerosis (SSc).

~~114. The use of claim 113, wherein the TGF β -related disorder is fibrosis, wherein, optionally, the fibrosis is a fibrotic condition of the lung, liver, heart, kidney, pancreas, eye, and/or skin.~~

~~115. Use of an antibody of any one of claim 1—claim 97 in the manufacture of a medicament for inhibiting TGFBR-dependent SMAD signaling, for inhibiting the assembly of TGF β TGFBR signaling complexes, for inhibiting TGF β signaling through the TGFBR1/R2 complex, for inhibiting TGF β signaling through the TGFBR2/ALK1 complex facilitated by endoglin, and/or for inhibiting new collagen synthesis.~~

~~116~~27. ~~A method of treating a subject having a TGF β -related disorder, the method comprising administering~~ The use according to claim 26, wherein an effective amount of the antibody of any one of claim 1 to claim 16 is to be administered to a ~~the~~ subject in need thereof ~~an effective amount of the antibody of any one of claim 1—claim 97 or administering to the subject the pharmaceutical formulation of claim 104.~~

~~117. A method for inhibiting TGFBR-dependent SMAD signaling, inhibiting the assembly of TGF β TGFBR signaling complexes, inhibiting TGF β signaling through the TGFBR1/R2 complex, inhibiting TGF β signaling through the TGFBR2/ALK1 complex facilitated by endoglin, and/or for inhibiting new collagen synthesis in a subject, comprising administering to a subject in need thereof an effective amount of the antibody of any one of claim 1—claim 97 to inhibit TGFBR-dependent SMAD signaling, inhibiting the assembly of TGF β TGFBR signaling complexes, inhibiting TGF β signaling through the TGFBR1/R2 complex, inhibiting TGF β signaling through the TGFBR2/ALK1~~

~~complex facilitated by endoglin and/or for inhibiting new collagen synthesis in the subject.~~

~~11828. The method of claim 116 of claim 117, The use according to any one of claim 26 to claim 27, wherein further comprising administering an additional therapeutic agent is to~~
5 ~~be further administered to the subject, optionally wherein the additional therapeutic agent is selected from the group consisting of pirfenidone, nintedanib, mycophenylate mofetil, an IL-6 inhibitor (e.g., tocilizumab, sarilumab), an anti-CTFG antibody (e.g., FG-3019), an autotaxin inhibitor, and PTX2.~~

~~119. The method of claim 118, wherein the additional therapeutic agent is selected from~~
10 ~~the group consisting of pirfenidone, nintedanib, mycophenylate mofetil, an IL-6 inhibitor (e.g., tocilizumab, sarilumab), an anti-CTFG antibody (e.g., FG-3019), an autotaxin inhibitor, and PTX2.~~

~~120. The method of any one of claim 116 to claim 119, comprising administering the subject an effective amount of an anti-TGF β 3 antibody according to claim 1 and an~~
15 ~~effective amount of an anti-TGF β 2 antibody according to claim 68.~~

~~121. The method of any one of claim 116 to claim 120, wherein the subject has a TGF β -related disorder that is fibrosis.~~

~~122. The method of claim 121, wherein the fibrosis is a lung fibrosis selected from the group consisting of idiopathic pulmonary fibrosis (IPF), idiopathic pulmonary upper lobe~~
20 ~~fibrosis (Amitani disease), familial pulmonary fibrosis, pulmonary fibrosis (e.g., pulmonary fibrosis secondary to systemic inflammatory diseases such as, rheumatoid arthritis, scleroderma, lupus, cryptogenic fibrosing alveolitis, chronic obstructive pulmonary disease (COPD) or chronic asthma), cystic fibrosis, non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), progressive massive~~
25 ~~fibrosis, scleroderma/systemic sclerosis (SSc, including limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) forms and SSc-associated interstitial lung disease (SSc-ILD)), bronchiolitis obliterans organizing pneumonia, connective tissue disease-associated ILD (CT-ILD), hypersensitivity pneumonitis, pulmonary hypertension, pulmonary tuberculosis, silicosis, asbestosis, acute lung injury, and acute respiratory distress (ARD,~~
30 ~~including bacterial pneumonia induced, trauma induced, and viral pneumonia induced, ventilator-induced, non-pulmonary sepsis induced).~~

123. The method of claim 121, wherein the fibrosis is a fibrotic condition of the liver selected from the group consisting of liver cirrhosis, congenital hepatic fibrosis, obesity, fatty liver, alcohol induced liver fibrosis, non alcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC),
5 infection or viral induced liver fibrosis (e.g., chronic hepatitis B and C virus infections), cystic fibrosis, autoimmune hepatitis, necrotizing hepatitis, primary sclerosing cholangitis, hemochromatosis, disorders of the biliary tree, and hepatic dysfunction attributable to infections.
124. The method of claim 121, wherein the fibrosis is a fibrotic condition of the heart
10 and/or pericardium selected from the group consisting of endomyocardial fibrosis, cardiac allograft vasculopathy (CAV), myocardial infarction, atrial fibrosis, congestive heart failure, arteriosclerosis, atherosclerosis, vascular stenosis, myocarditis, congestive cardiomyopathy, coronary infarcts, varicose veins, coronary artery stenosis and other post-ischemic conditions, and idiopathic retroperitoneal fibrosis.
125. The method of claim 121, wherein the fibrosis is a fibrotic condition of the kidney
15 selected from the group consisting of glomerulonephritis (including membranoproliferative, diffuse proliferative, rapidly progressive or sclerosing, post-infectious and chronic forms), diabetic glomerulosclerosis, focal segmental glomerulosclerosis, IgA nephropathy, diabetic nephropathy, ischemic nephropathy,
20 tubulointerstitial kidney fibrosis, HIV associated nephropathy, membrane nephropathy, glomerulonephritis secondary to systemic inflammatory diseases such as lupus, scleroderma and diabetes glomerulonephritis, idiopathic membranoproliferative glomerular nephritis, mesangial proliferative glomerulonephritis, crescentic glomerulonephritis, amyloidosis (which affects the kidney among other tissues),
25 autoimmune nephritis, renal tubulointerstitial fibrosis, renal arteriosclerosis, Alport's syndrome, nephrotic syndrome, chronic renal failure, chronic kidney disease, periglomerular fibrosis/atubular glomeruli, combined apical emphysema and basal fibrosis syndrome (emphysema/fibrosis syndrome), glomerular hypertension, nephrogenic fibrosing dermatopathy, polycystic kidney disease, Fabry's disease, and renal
30 hypertension.
126. The method of claim 121, wherein the fibrosis is a fibrotic condition of the pancreas selected from the group consisting of stromal remodeling pancreatitis and stromal fibrosis.

- ~~127. The method of claim 121, wherein the fibrosis is a fibrotic condition of the gastrointestinal tract selected from the group consisting of Crohn's disease, ulcerative colitis, collagenous colitis, colorectal fibrosis, villous atrophy, crypt hyperplasia, polyp formation, healing gastric ulcer, and microscopic colitis.~~
- 5 ~~128. The method of claim 121, wherein the fibrosis is a fibrotic condition of the eye selected from the group consisting of ocular fibrosis, ophthalmic fibrosis, proliferative vitreoretinopathy, vitreoretinopathy of any etiology, fibrosis associated with retinal dysfunction, fibrosis associated with wet or dry macular degeneration, scarring in the cornea and conjunctiva, fibrosis in the corneal endothelium, anterior subcapsular cataract~~
- 10 ~~and posterior capsule opacification, anterior segment fibrotic diseases of the eye, fibrosis of the corneal stroma (e.g., associated with corneal opacification), fibrosis of the trabecular network (e.g., associated with glaucoma), posterior segment fibrotic diseases of the eye, fibrovascular scarring (e.g., in retinal or choroidal vasculature of the eye), retinal fibrosis, epiretinal fibrosis, retinal gliosis, subretinal fibrosis (e.g., associated with age~~
- 15 ~~related macular degeneration), tractional retinal detachment in association with contraction of the tissue in diabetic retinopathy, congenital orbital fibrosis, lacrimal gland fibrosis, corneal subepithelial fibrosis, and Grave's ophthalmopathy.~~
- ~~129. The method of claim 121, wherein the fibrosis is selected from fibrosis resulting from spinal cord injury/fibrosis or central nervous system fibrosis such as fibrosis after a~~
- 20 ~~stroke, Duchenne muscular dystrophy, fibrosis associated with neurodegenerative disorder such as Alzheimer's disease or multiple sclerosis, vascular restenosis, uterine fibrosis, endometriosis, ovarian fibroids, Peyronie's disease, polycystic ovarian syndrome, disease related pulmonary apical fibrosis in ankylosing spondylitis, scarring, and fibrosis incident to microbial infections (e.g., bacterial, viral, parasitic, fungal).~~
- 25 ~~130. The method of claim 121, wherein the fibrosis is SSc.~~
- ~~131. The method of claim 121, wherein the fibrosis is IPF.~~
- ~~132. The method of claim 121, wherein the fibrosis is chronic obstructive pulmonary disease (COPD).~~
- ~~133. The method of claim 121, wherein the fibrosis is progressive fibrosing interstitial~~
- 30 ~~lung disease (PF-ILD).~~

- ~~134. The method of claim 133, wherein the PF-ILD is a disease or condition selected from the group consisting of non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), progressive massive fibrosis, a complication of coal worker's pneumoconiosis, scleroderma/systemic sclerosis, bronchiolitis obliterans organizing pneumonia; connective tissue disease associated ILD (CT-ILD), and hypersensitivity pneumonitis.~~
- ~~135. The method of claim 121, wherein the fibrosis is liver cirrhosis or chronic hepatic fibrosis.~~
- ~~136. The method of claim 121, wherein the fibrosis is GI tract fibrosis, e.g., intestinal fibrosis, optionally, selected from the group consisting of fibrosis associated with Crohn's disease, ulcerative colitis, collagenous colitis, colorectal fibrosis, villous atrophy, crypt hyperplasia, polyp formation, healing gastric ulcer, and microscopic colitis.~~
- ~~137. The method of claim 121, wherein the fibrosis is a fibrotic condition of the eye, fibrosis resulting from spinal cord injury, fibrosis or central nervous system fibrosis, or fibrosis associated with a neurodegenerative disorder.~~
- ~~138. The method of any one of claim 116 to claim 137, wherein the antibody is an anti-TGF β 2 antibody.~~
- ~~139. The method of claim 138, wherein the anti-TGF β 2 antibody comprises:~~
- ~~(a) heavy chain CDRs comprising CDR H1, H2 and H3, wherein CDR H1 has the amino acid sequence of SEQ ID NO: 16, CDR H2 has the amino acid sequence of SEQ ID NO: 17, and CDR H3 has the amino acid sequence of SEQ ID NO: 18; and (b) light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 19; CDR L2 has the amino acid sequence of SEQ ID NO: 20, and CDR L3 has the amino acid sequence of SEQ ID NO: 21.~~
- ~~140. The method of any one of claim 116 to claim 137, wherein the antibody is an anti-TGF β 3 antibody.~~
- ~~141. The method of claim 140, wherein the anti-TGF β 3 antibody comprises:~~
- ~~(a) (i) heavy chain CDRs comprising CDR H1, H2 and H3, wherein CDR H1 has the amino acid sequence of SEQ ID NO: 4, CDR H2 has the amino acid sequence of one of SEQ ID NO: 35, and CDR H3 has the amino acid sequence of SEQ ID NO: 6; and (ii)~~

light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 7; CDR L2 has the amino acid sequence of SEQ ID NO: 8, and CDR L3 has the amino acid sequence of SEQ ID NO: 9;

(b) a VH/VL pair, the VH of the VH/VL pair comprising the amino acid sequence of SEQ ID NO: 57, and the VL of the VH/VL pair comprising the amino acid sequence of SEQ ID NO: 56; or

(c) a complete H/L chain pair, the H chain of the H/L chain pair comprising the amino acid sequence of SEQ ID NO: 79 and the L chain of the H/L chain pair comprising the amino acid sequence of SEQ ID NO: 78.

142. The method of any one of claim 116 to claim 137, wherein the antibody is an anti-TGF β 2/3 antibody.

143. The method of claim 142, wherein the anti-TGF β 2/3 antibody comprises: (i) heavy chain CDRs comprising CDR H1, H2 and H3, wherein CDR H1 has the amino acid sequence of SEQ ID NO: 10, CDR H2 has the amino acid sequence of SEQ ID NO: 11, and CDR H3 has the amino acid sequence of SEQ ID NO: 12; and (ii) light chain CDRs comprising CDR L1, L2 and L3, wherein CDR L1 has the amino acid sequence of SEQ ID NO: 13; CDR L2 has the amino acid sequence of SEQ ID NO: 14, and CDR L3 has the amino acid sequence of SEQ ID NO: 15;

144. A method of diagnosing a subject as having SSc, the method comprising detecting the expression levels of the genes in an 18 gene signature set consisting of PRSS23, PXDN, COL8A1, COL6A3, SERPINE2, TNC, COMP, THBS1, COL11A1, COL1A1, COL5A2, COL1A2, COL4A1, COL4A2, SFRP4, ALPK2, COL5A1, and TAGLN, and diagnosing the subject with SSc if the levels of the genes are determined to be elevated relative to the gene levels in a healthy control set or reference gene signature.

145. The method of claim 144, wherein a gene level is elevated if the expression increase relative to the healthy control set or reference gene signature is statistically significant, optionally, at least two fold increased, or at least three fold increased, or at least four fold increased, relative to the healthy control set or reference gene signature.

146. A method of monitoring response to treatment of a subject with an anti-TGF β 2 antibody and/or an anti-TGF β 3 antibody, the method comprising determining the expression level of one or more of the TGF β -inducible genes selected from the group

consisting of *serpine1*, *coll1a1*, *coll1a2*, and *col3a1* in a sample from the subject, wherein the subject has received one or more administrations of the anti-TGF β 2 antibody and/or the anti-TGF β 3 antibody.

147. The method of claim 146, wherein the subject is determined to be responding to treatment with the anti-TGF β 2 antibody and/or anti-TGF β 3 antibody, if the expression level of the one or more TGF β inducible genes is significantly reduced compared to pre-treatment levels of the one or more TGF β inducible genes, wherein optionally the method further comprises administering an additional administration of the anti-TGF β 2 antibody and/or the anti-TGF β 3 antibody if the expression level of the one or more TGF β inducible genes is determined to be significantly reduced.

148. The method of claim 146 or claim 147, wherein the subject is administered the anti-TGF β 2 antibody as a monotherapy.

149. The method of claim 146 or claim 147, wherein the subject is administered the anti-TGF β 3 antibody as a monotherapy.

150. The method of claim 146, wherein the expression level of the one or more TGF β inducible genes is determined by qPCR or microarray analysis.

15129. The method or use of any one of claim 98 to claim 150 use according to any one of claim 26 to claim 28, wherein the subject is a human.

15230. A kit comprising an antibody of any one of claim 1 to claim 1697.