

CLAIMS

What is claimed is:

1. An anti-transforming growth factor beta 3 (TGF β 3) antibody comprising a VH/VL pair comprising amino acid sequences (respectively) of SEQ ID NOs: 57/56 (v4).
- 5 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
10 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;
 - 15 (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-TGF β 3 antibody directly contacts amino acid residue R394 in the beta6/beta7 hairpin region of human TGF β 3 and residue R394 of TGF β 3 makes an ionic salt bridge with the anti-TGF β 3 antibody in the heavy chain CDR2;
 - 20 (f) isoform selectivity of the anti-TGF β 3 antibody for TGF β 3 over TGF β 1 is achieved by direct contact by the antigen binding domain of the anti-TGF β 3 antibody with amino acid residues T387, L389, and T395 of TGF β 3 (human TGF β 3 numbering);
 - (g) the isoform selectivity of the anti-TGF β 3 antibody for TGF β 3 over TGF β 2 is achieved by direct contact by the antigen binding domain of the anti-TGF β 3 antibody with amino
25 acid residues R325, R394, and V398 of TGF β 3 (human TGF β 3 numbering);

- (h) 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
- (i) the anti-TGFβ3 antibody as in (h), 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.
4. The anti-TGFβ3 antibody of any of claim 1 to claim 3, 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 of SEQ ID NO: 79.
5. The anti-TGFβ3 antibody of any of claim 1 to claim 4, wherein the antibody comprises a complete heavy (H) chain amino acid sequence of SEQ ID NO: 79.
6. The anti-TGFβ3 antibody of any of claim 1 to claim 5, 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 of SEQ ID NO: 78.
7. The anti-TGFβ3 antibody of any of claim 1 to claim 6, wherein the antibody comprises a complete L chain amino acid sequence of SEQ ID NO: 78.
8. The anti-TGFβ3 antibody of any of claim 1 to claim 7, wherein the antibody comprises a complete H/L chain pair comprising amino acid sequences (respectively) of SEQ ID NOs: 79/78 (v4).
9. The anti-TGFβ3 antibody of any one of claim 1 to claim 8, wherein the antibody specifically binds to human TGFβ3, optionally wherein the antibody specifically binds to both the immature and mature forms of TGFβ3.
10. The antibody of any one of claim 1 to claim 9, which is a monoclonal antibody.
11. The antibody of any one of claim 1 to claim 9, which is a human, humanized, or chimeric antibody.
12. The antibody of any one of claim 1 to claim 9, which is an antibody fragment.

13. The antibody of any one of claim 1 to claim 9, 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.
14. The antibody of claim 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.
15. The antibody of any one of claim 13 to claim 14, wherein the Fc region is modified to remove effector function.
16. The antibody of any one of claim 1 to claim 15, wherein the antibody has a C_{max} of about 230-260 µg/ml and/or a half life (t_{1/2}) of about 15 to 16 days.
17. A nucleic acid encoding the antibody of any one of claim 1 to claim 16.
18. A host cell comprising the nucleic acid of claim 17.
19. A method of producing an antibody comprising culturing the host cell of claim 18, so that the antibody is produced.
20. The method of claim 19, further comprising recovering the antibody from the host cell.
21. An antibody produced by the method of claim 19 or claim 20.
22. An immunoconjugate comprising the antibody of any one of claim 1 to claim 16 and a cytotoxic agent.
23. A pharmaceutical formulation comprising the antibody of any one of claim 1 to claim 16, or the immunoconjugate of claim 22 and a pharmaceutically acceptable carrier.
24. The pharmaceutical formulation of claim 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 autotaxin inhibitor, a JAK inhibitor, an IL-11 inhibitor, and PTX2.

25. The antibody of any one of claim 1 to claim 16, for use as a medicament.
26. Use of the antibody according to any one of claim 1 to claim 16 in the manufacture of a medicament for 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
- 5 scleroderma/systemic sclerosis (SSc).
27. 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 the subject in need thereof.
28. The use according to any one of claim 26 to claim 27, wherein an additional therapeutic agent is to be further administered to the subject, optionally wherein the
- 10 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.
29. The use according to any one of claim 26 to claim 28, wherein the subject is a human.
30. A kit comprising an antibody of any one of claim 1 to claim 16.

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