

selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D \leq 25$ nM. In one example, the disclosure provides isoform-specific TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D \leq 10$ nM. In one example, the disclosure provides an isolated antibody, or antigen-binding portion thereof, that selectively binds to a LTBP1-proTGFβ1 complex and a LTBP3-proTGFβ1 complex, wherein the antibody, or antigen-binding portion thereof, does not bind to one or more of the following targets: (a) LTBP1 alone; (b) proTGFβ1 alone; (c) a GARP-proTGFβ1 complex; and (d) a LRRC33-proTGFβ1 complex. In further examples, the disclosure provides isoform-specific TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D < 5$ nM.

[022] In one example, the disclosure provides inhibitors of extracellular matrix-associated TGFβ activation, which selectively bind a LTBP1/3-presented proTGFβ latent complex. In one example, the inhibitor does not inhibit immune cell-associated TGFβ1 activation, for example, immune cell-associated TGFβ1 activation that results from activation of a GARP-presented proTGFβ1 latent complex. In exemplary examples, the inhibitor is an antibody, or antigen-binding portion thereof.

[022a] In one aspect, the present disclosure refers to an antibody, or antigen-binding fragment thereof, which specifically binds human LTBP1-TGFβ1 complex and human LTBP3-TGFβ1 complex as measured by biolayer interferometry-based in vitro binding assay (BLI), comprising the following six CDRs: a) CDR-H1 comprising the amino acid sequence FTFRSYVMH; b) CDR-H2 comprising the amino acid sequence (VISHEGSLKYYADSVKG; and c) CDR-H3 comprising the amino acid sequence ARPRIAARRGGFGY; d) CDR-L1 comprising TRS(X1)G(X2)ID(X3)NYVQ, wherein, X1 is S or H; X2 is N or A; and X3 is N, D or Y; e) CDR-L2 comprising the amino acid sequence ED(X1)(X2)RPS, wherein: X1 is N, or F; and X2 is Q or V; and f) CDR-L3 comprising the amino acid sequence QSYD(X1)(X2)(X3)Q(X4)VV, wherein: X1 is S, Y or D; X2 is S or D; X3 is N, L or T; and X4 is G, R, A or L.

[023] In other examples, the disclosure provides TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ complex and/or a LTBP3-TGFβ complex. In some examples, the antibodies, or antigen-binding fragments thereof, selectively bind to LTBP1-TGFβ1. In some examples, such antibodies bind both human and murine counterparts.

[024] In one example, the disclosure provides an isolated antibody, or antigen-binding portion thereof, that selectively binds an LTBP1-proTGFβ latent complex and/or an LTBP3-proTGFβ latent complex, thereby modulating release of mature TGFβ growth factor from the latent complex, wherein the antibody, or antigen-binding portion thereof, does not bind mature TGFβ1 alone or a GARP-proTGFβ1 latent complex. In one example, the antibody, or antigen-binding portion thereof, does not bind an LRRC33-proTGFβ1 latent complex. Alternatively, in one example, the antibody, or antigen-binding portion thereof, binds an LRRC33-proTGFβ1 latent complex.

CLAIMS

What is claimed is:

1. An antibody, or antigen-binding fragment thereof, which specifically binds human LTBP1-TGF β 1 complex and human LTBP3-TGF β 1 complex as measured by biolayer interferometry-based in vitro binding assay (BLI), comprising the following six CDRs:

- a) CDR-H1 comprising the amino acid sequence FTFRSYVMH;
- b) CDR-H2 comprising the amino acid sequence VISHEGSLKYYADSVKG; and
- c) CDR-H3 comprising the amino acid sequence ARPRIAARRGGFGY;
- d) CDR-L1 comprising the amino acid sequence TRS(X1)G(X2)ID(X3)NYVQ,

wherein, X1 is S or H; X2 is N or A; and X3 is N, D or Y;

e) CDR-L2 comprising the amino acid sequence ED(X1)(X2)RPS, wherein: X1 is N, or F; and X2 is Q or V; and

f) CDR-L3 comprising the amino acid sequence QSYD(X1)(X2)(X3)Q(X4)VV,
wherein: X1 is S, Y or D; X2 is S or D; X3 is N, L or T; and X4 is G, R, A or L.

2. The antibody, or antigen-binding fragment thereof according to claim 1, wherein the antibody comprises:

a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 318; and

a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 319.

3. The antibody, or antigen-binding fragment thereof according to claim 1, wherein the antibody comprises:

a heavy chain variable region having an amino acid sequence that is set forth as SEQ ID NO: 318; and

a light chain variable region having an amino acid sequence that is set forth as SEQ ID NO: 319.

4. The antibody, or antigen-binding fragment thereof, according to claim 1 or claim 2, wherein:

- a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 166;
- b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 167;
- c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 168;
- d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 169;
- e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 170; and

- f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 171.
5. The antibody, or antigen-binding fragment thereof, according to claim 1 or claim 2, wherein:
- a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 154;
 - b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 155;
 - c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 156;
 - d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 157;
 - e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 158; and
 - f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 159.
6. The antibody, or antigen-binding fragment thereof, according to claim 1 or claim 2, wherein:
- a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 160;
 - b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 161;
 - c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 162;
 - d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 163;
 - e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 164; and
 - f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 165.
7. The antibody, or antigen-binding fragment thereof, according to claim 1 or claim 2, wherein:
- a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 172;
 - b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 173;
 - c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 174;
 - d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 175;
 - e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 176; and
 - f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 177.
8. The antibody, or antigen-binding fragment thereof, according to claim 1 or claim 2, wherein:
- a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 178;
 - b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 179;
 - c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 180;
 - d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 181;
 - e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 182; and
 - f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 183.
9. The antibody, or antigen-binding fragment thereof, according to claim 1 or claim 2, wherein:
- a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 184;
 - b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 185;

- c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 186;
 - d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 187;
 - e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 188; and
 - f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 189.
10. The antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, which comprises the CDR sequences:
- i) CDR-H1 as set forth in SEQ ID NO: 116;
 - ii) CDR-H2 as set forth in SEQ ID NO: 117; and;
 - iii) CDR-H3 as set forth in SEQ ID NO: 118;
 - iv) CDR-H1 as set forth in SEQ ID NO: 119;
 - v) CDR-H2 as set forth in SEQ ID NO: 120; and
 - vi) CDR-H3 as set forth in SEQ ID NO: 121..
11. The antibody, or antigen-binding fragment thereof, according claim 1 or claim 2, which has a variable heavy chain sequence as set forth in SEQ ID NO: 122.
12. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which binds a human LTBP1-proTGF β 1 complex and a human LTBP3-TGF β 1 complex with a K_D of < 5 nM as measured by Bio-Layer Interferometry (BLI), optionally < 1nM.
13. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which is cross-reactive with mouse LTBP1-proTGF β 1.
14. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which is cross-reactive with mouse LTBP3-proTGF β 1.
15. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP1-proTGF β 1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).
16. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP3-proTGF β 1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

17. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or antigen-binding fragment thereof cross-reacts with human and murine LTBP1-proTGF β 1 and LTBP3-proTGF β 1 complexes, each with a KD of < 5 nM or optionally < 1 nM.
18. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody is an IgG4 or IgG1 subtype, optionally wherein the antibody is a human IgG4 subtype and comprises a backbone substitution of Ser to Pro that produces an IgG1-like hinge.
19. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or the antigen-binding fragment thereof comprises a mutation in a constant region.
20. A pharmaceutical composition comprising the antibody of any one of the preceding claims and a pharmaceutically acceptable excipient.
21. The pharmaceutical composition according to claim 20, which is prepared for intravenous administration or subcutaneous administration.
22. A composition comprising a multi-dose vial containing the pharmaceutical composition of claim 20 or 21.
23. A composition comprising a single-dose syringe containing the pharmaceutical composition of claim 20 or 21, optionally wherein the syringe is a disposable syringe.
24. Use of the composition of any one of claims 20-23 in the manufacture of a medicament for treating a fibrotic disorder in a human subject.
25. The use according to claim 24, wherein the fibrotic disorder is an organ fibrosis.
26. The use according to claim 25, wherein the organ fibrosis is an advanced organ fibrosis.
27. The use according to claim 25 or 26, wherein the organ fibrosis is selected from the group consisting of: kidney fibrosis, liver fibrosis, lung fibrosis, cardiac fibrosis, pancreatic fibrosis, skin fibrosis, scleroderma, muscle fibrosis, uterine fibrosis and endometriosis.

28. The use according to claim 27, wherein the lung fibrosis is idiopathic pulmonary fibrosis (IPF).
29. The use according to claim 27, wherein the subject has chronic kidney disease (CKD).
30. The use according to claim 27, wherein the liver fibrosis is associated with nonalcoholic steatohepatitis (NASH).
31. The use according to claim 27, wherein the kidney fibrosis is selected from IgA nephropathy, focal and segmental glomerulosclerosis, crescentic glomerulonephritis, lupus nephritis and diabetic nephropathy.
32. The use according to any one of claims 24-31, wherein the medicament is to be administered to the subject at a dosage of between 0.1 and 30 mg/kg.
33. The use according to claim 32, wherein the medicament is to be administered twice a week, once a week, once every 2 weeks, once every 3 weeks, once a month, or every other month.
34. The use according to claim 32, wherein a therapeutic regimen comprises an initial phase of a therapy and a subsequent phase of the therapy, wherein the subject receives a loading dose during the initial phase followed by a maintenance dose during the subsequent phase.
35. The use according to claim 32, wherein the loading dose is between 2-30 mg/kg, and the maintenance dose is between 0.1-20 mg/kg.
36. The use according to claim 24 or 35, wherein the loading dose is to be administered to the subject twice a week or once a week.
37. The use according to any one of claims 34-36, wherein the maintenance dose is to be administered to the subject once every 2-8 weeks.
38. The use according to any one of claims 24-37, wherein the use further comprises testing or confirming expression of TGF β 1, LTBP1 or LTBP3 in a biological sample collected from the subject.
39. A method for making a composition of any one of claims 20-23, comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGF β 1 complex and a human LTBP3-proTGF β 1 complex, wherein the antibody, or the antigen-binding fragment thereof, does not show detectable binding to a human GARP-proTGF β 1 or human LRRC33-proTGF β 1 complex, the method comprising steps of:

i) selecting an antibody or an antigen-binding fragment thereof that dissociates from a human LTBP1-proTGFβ1 complex and a human LTBP3-proTGFβ1 complex with $t_{1/2}$ of at least 45 minutes, and dissociates from a human GARP-proTGFβ1 and/or a human LRRC33-proTGFβ1 complex with $t_{1/2}$ of 5 minutes or less; and,

ii) formulating the antibody or antigen-binding fragment into a pharmaceutical composition, thereby making the composition comprising the antibody or antigen-binding fragment.

40. The method of claim 39, further comprising the step of: selecting an antibody or antigen-binding fragment with IC₅₀ of < 5 nM as measured by cell-based assays, optionally < 2 nM.

41. The method of any one of claims 39-40, wherein the method further comprises a step of: selecting antibodies or fragments that are cross-reactive to human and rodent antigens.

42. The method of any one of claims 39-41, wherein the method further comprises a step of: subjecting the selected antibody or selected antigen-binding fragment to affinity maturation and/or optimization, so as to provide an affinity matured and/or optimized antibody or antigen-binding fragment.

43. The composition of any one of claims 20-23 for use in therapy.