

inflammation; b) the subject benefits from immune suppression; c) the subject has or is at risk of developing an autoimmune disease; d) the subject is a candidate for or has received an allograft transplant; e) the subject has an elevated Th17/Treg ratio; and/or, f) the subject is in need of a long-term or chronic administration of the TGFβ1 inhibitor. In some examples, the the subject has or is at risk of developing a metabolic disorder (and the subject is optionally a subject according to one or more of a)-f)). In some examples, the the antibody, or antigen-binding fragment thereof, is an isoform-specific LTBP1-proTGFβ1 inhibitor and/or LTBP3-proTGFβ1 inhibitor.

[046] The antibodies or antigen-binding fragments thereof provided herein may be used in a method for treating a fibrotic disorder in a subject. The fibrotic disorder may comprise chronic inflammation. The subject may benefit from immune suppression. The subject may have or be at risk of developing an autoimmune disease. The subject may be a candidate for or may have received an allograft transplant.

[047] Alternatively, or in addition, the subject may have an elevated Th17/Treg ratio. The subject may be in need of a long-term or chronic administration of the TGFβ1 inhibitor.

[048] Alternatively, or in addition, the subject may have or be at risk of developing a metabolic disorder.

[048a] In another aspect, the present disclosure refers to a method for making a composition as disclosed herein, comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, wherein the antibody, or the antigen-binding fragment thereof, does not show detectable binding to a human GARP-proTGFβ1 or human LRRC33-proTGFβ1 complex, the method comprising steps of: i) selecting an antibody or an antigen-binding fragment thereof that dissociates from human LTBP1-proTGFβ1 complex and/or 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.

[049] In another example, the disclosure provides a method for making a composition comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody, or antigen-binding fragment thereof, inhibits TGFβ1 but does not inhibit TGFβ2 or TGFβ3, the method comprising steps of i) providing at least one antigen comprising LTBP1-proTGFβ1 and/or LTBP3-proTGFβ1, ii) selecting a first pool of antibodies, or antigen-binding fragments thereof, that specifically bind the at least one antigen of step (i) so as to provide specific binders of LTBP1-proTGFβ1 and/or LTBP3-proTGFβ1; iii) selecting a second pool of antibodies, or antigen-binding fragments thereof, that inhibit activation of TGFβ1, so as to generate specific inhibitors of TGFβ1 activation; iv) formulating an antibody, or antigen-binding fragment thereof, that is present in the first pool of antibodies and the second pool of antibodies into a pharmaceutical composition, thereby making the composition comprising the antibody, or antigen-binding fragment thereof.

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, comprising the following six CDRs:
 - a) CDR-H1 comprising the amino acid sequence FTF(X₁)(X₂)YVMH, wherein: X₁ is S or R; and X₂ is G or S;
 - b) CDR-H2 comprising the amino acid sequence (X₁)ISHEGS(X₂)KYYADSVKG, wherein: X₁ is V or S; X₂ is F or L; and
 - c) CDR-H3 comprising the amino acid sequence ARPRI(X₁)ARRGGFGY, wherein X₁ is A or L ;
 - d) CDR-L1 as set forth in SEQ ID NO:97, comprising up to three amino acid changes;
 - e) CDR-L2 as set forth in SEQ ID NO:98, comprising up to three amino acid changes;and
 - f) CDR-L3 as set forth in SEQ ID NO:99, comprising up to three amino acid changes.
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: 88; and
 - a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 89.
3. The antibody, or antigen-binding fragment thereof, according to claim 1 or 2, wherein the up to three amino acid changes comprises up to two amino acid changes.
4. The antibody, or antigen-binding fragment thereof, according to any one of claims 1-3, 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, of claim 1, 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.
6. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which has a variable heavy chain sequence as set forth in SEQ ID NO: 122.
7. 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.
- ~~318~~8. 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.
- ~~89~~9. 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.
- ~~910~~10. 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).
- ~~1011~~11. 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).
- ~~1112~~12. 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 K_D of < 5 nM or optionally < 1 nM.
- ~~1213~~13. 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.

~~13~~14. The antibody, or antigen-binding fragment thereof, according to any one of the ~~proceeding~~ preceding claims, wherein the antibody, or the antigen-binding fragment thereof comprises a mutation in a constant region.

~~14~~15. A pharmaceutical composition comprising the antibody of any one of the preceding claims and a pharmaceutically acceptable excipient.

~~15~~16. The pharmaceutical composition according to claim ~~14~~15, which is prepared for intravenous administration or subcutaneous administration.

~~17~~16. A composition comprising a multi-dose vial containing the pharmaceutical composition of claim ~~14~~15 or ~~15~~16.

~~17~~18. A composition comprising a single-dose syringe containing the pharmaceutical composition of claim ~~14~~15 or ~~15~~16, optionally wherein the syringe is a disposable syringe.

~~19~~18. Use of the composition of any one of claims ~~14~~15-~~17~~18 in the manufacture of a medicament for treating a fibrotic disorder in a human subject.

~~19~~20. The use according to claim ~~18~~19, wherein the fibrotic disorder is an organ fibrosis.

~~20~~21. The use according to claim ~~19~~20, wherein the organ fibrosis is an advanced organ fibrosis.

~~21~~22. The use according to claim ~~19~~20 or ~~20~~21, 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.

~~22~~23. The use according to claim ~~21~~22, wherein the lung fibrosis is idiopathic pulmonary fibrosis (IPF).

~~23~~24. The use according to claim ~~21~~22, wherein the subject has chronic kidney disease (CKD).

~~24~~25. The use according to claim ~~21~~22, wherein the liver fibrosis is associated with nonalcoholic steatohepatitis (NASH).

~~25~~26. The use according to any one of claims ~~18~~19-~~24~~25, wherein the medicament is to be administered to the subject at a dosage of between 0.1 and 30 mg/kg.

~~26~~27. The use according to claim ~~25~~26, 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.

~~27~~28. The use according to claim ~~25~~26, 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.

~~28~~29. The use according to claim ~~28~~27, wherein the loading dose is between 2-30 mg/kg, and the maintenance dose is between 0.1-20 mg/kg.

~~29~~30. The use according to claim ~~27~~28 or ~~28~~29, wherein the loading dose is to be administered to the subject twice a week or once a week.

~~30~~31. The use according to any one of claims ~~27~~28-~~29~~30, wherein the maintenance dose is to be administered to the subject once every 2-8 weeks.

~~31~~32. The use according to any one of claims ~~18~~19-~~30~~31, wherein the use further comprises testing or confirming expression of TGF β 1, LTBP1 or LTBP3 in a biological sample collected from the subject.

~~32~~33. A method for making a composition of any one of claims ~~14~~15-~~17~~18, comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGF β 1 complex and ~~or~~ 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-proTGF β 1 complex and ~~or~~ a human LTBP3-proTGF β 1 complex with t $\frac{1}{2}$ of at least 45 minutes, and dissociates from a human GARP-proTGF β 1 and/or a human LRRC33-proTGF β 1 complex with t $\frac{1}{2}$ 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.

~~33~~34. The method of claim ~~32~~33, 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.

34. ~~The method of claim 32 or 33, further comprising the step of: confirming efficacy in an in vivo preclinical model, wherein optionally the preclinical model is a liver fibrosis model, kidney fibrosis model, or cardiac fibrosis model.~~

35. The method of any one of claims ~~3233~~-34, wherein the method further comprises a step of: selecting antibodies or fragments that are cross-reactive to human and rodent antigens.

36. The method of any one of claims ~~3233~~-35, wherein the method further comprises a step of: subjecting the selected antibody or selected antigen-binding fragment ~~that is present in the first pool of antibodies and the second pool of antibodies~~ to affinity maturation and/or optimization, so as to provide an affinity matured and/or optimized antibody or antigen-binding fragment.

37. The composition of any one of claims ~~4415-47~~15-18 for use in therapy.