

We Claim:

1. An isolated antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen binding fragment specifically binds to human proTGF $\beta$ 1 in a complex with human glycoprotein A repetitions predominant (proTGF $\beta$ 1-GARP complex) while said complex is in solution and the antibody or antigen binding fragment thereof has no detectable binding according to the biolayer interferometry assay using the experimental design described in Example 4 to any of the following agents :
  - a TGF $\beta$ 1 growth factor domain,
  - a TGF $\beta$ 2 growth factor domain,
  - a TGF $\beta$ 3 growth factor domain,
  - proTGF $\beta$ 1 covalently associated with LTBP1,
  - proTGF $\beta$ 1 covalently associated with LTBP3,
  - proTGF $\beta$ 1 covalently associated with LRRC33, and
  - proTGF $\beta$ 1 that is unassociated with human GARP,as measured by OctetRed 384 under the conditions shown in Examples 4 and 6 and further wherein the antibody or antigen-binding fragment thereof has an inhibitory concentration (IC<sub>50</sub>) of less than or equal to 10 nM for inhibition of TGF $\beta$ 1 growth factor release from a cell-associated proTGF $\beta$ 1-GARP complex under the conditions shown in Example 5.
2. The antibody or antigen-binding fragment of claim 1 wherein the antibody or antigen-binding fragment inhibits Treg function *in vitro*.
3. The antibody or antigen-binding fragment of any of claims 1 and 2, wherein the antibody or antigen binding fragment thereof inhibits the activation of TGF $\beta$ 1.
4. The antibody or antigen-binding fragment of any one of claims 1 to 3, wherein the antibody or antigen binding fragment thereof binds to an epitope of human proTGF $\beta$ 1 modified as a result of complex formation with human GARP.
5. The antibody or antigen-binding fragment of any one of claims 1 to 4, wherein the antibody or antigen binding fragment thereof binds to a polypeptide having the amino acid sequence of SEQ ID NO: 2 in the presence of a polypeptide having the amino acid sequence of SEQ ID NO: 1.
6. The antibody or antigen-binding fragment of any one of claims 1 to 5, wherein the antibody or antigen-binding fragment thereof specifically binds to human

- proTGFβ1 with a binding affinity of at least 880 pM as measured by biolayer interferometry assay using the experimental design described in Example 4.
7. The antibody or antigen-binding fragment of any one of claims 1 to 5, wherein the antibody or antigen-binding fragment thereof binds to human proTGFβ1 with a dissociation constant (K<sub>d</sub>) of less than or equal to 1 nM for human proTGFβ1 in a complex with human glycoprotein A repetitions predominant (proTGFβ1-GARP complex) under the conditions shown in Example 7 and wherein said proTGFβ1-GARP complex is in solution.
  8. An isolated antibody, or an antigen-binding fragment thereof, comprising:
    - a. a heavy chain complementarity determining region (CDR)1 having the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 5, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 6, a light chain CDR1 having the amino acid sequence of SEQ ID NO: 7, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 8, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 9; or
    - b. a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 10, a heavy chain CDR2 having the amino acid sequence of SEQ ID NO: 11, and a heavy chain CDR3 having the amino acid sequence of SEQ ID NO: 12, a light chain CDR1 having the amino acid sequence of SEQ ID NO: 13, a light chain CDR2 having the amino acid sequence of SEQ ID NO: 14, and a light chain CDR3 having the amino acid sequence of SEQ ID NO: 15.
  9. An isolated antibody, or an antigen-binding fragment thereof, comprising a heavy chain sequence selected from the group consisting of the amino acid sequences of SEQ ID NOs: 16 and 18.
  10. The antibody of claim 9, comprising a light chain sequence selected from the group consisting of the amino acid sequences of SEQ ID NOs: 17 and 19.
  11. The antibody of claim 10, wherein
    - a. the heavy chain sequence comprises the amino acid sequence of SEQ ID NO: 16 paired with a light chain sequence comprising the amino acid sequence of SEQ ID NO: 17; or
    - b. the heavy chain sequence comprises the amino acid sequence of SEQ ID NO: 18 paired with a light chain sequence comprising the amino acid sequence of

SEQ ID NO: 19.

12. The antigen-binding fragment of any one of claims 1 to 11, wherein the antigen binding fragment is a Fab fragment, a Fab2 fragment, or a single chain antibody.
13. The antibody or antigen-binding fragment of any one of claims 1 to 12 wherein the antibody or antigen-binding fragment is recombinant.
14. The antibody or antigen-binding fragment of any one of claims 1 to 13 wherein the antibody or antigen-binding fragment thereof are of IgG1, IgG2, IgG3, or IgG4 isotype.
15. The antibody or antigen-binding fragment of any of claims 1 to 14, wherein the antibody is an IgG4 isotype.
16. An isolated antibody, or an antigen-binding fragment thereof, comprising:
  - a. a heavy chain CDR1 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 4, a heavy chain CDR2 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 5, and a heavy chain CDR3 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 6, a light chain CDR1 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 7, a light chain CDR2 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 8, and a light chain CDR3 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 9; or
  - b. a heavy chain CDR1 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 10, a heavy chain CDR2 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 11, and a heavy chain CDR3 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 12, a light chain CDR1 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 13, a light chain CDR2 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 14, and a light chain CDR3 sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 15.
17. An isolated antibody, or an antigen-binding fragment thereof, comprising:
  - a. a heavy chain sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 16 paired with a light chain sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 17; or

- b. a heavy chain sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 18 paired with a light chain sequence having at least 80% identity to the amino acid sequence of SEQ ID NO: 19.
18. An isolated antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable region sequence selected from the group consisting of amino acids 1-118 of the amino acid sequence of SEQ ID NO:16 and amino acids 1-121 of the amino acid sequence of SEQ ID NO: 18.
19. The antibody of claim 18, comprising a light chain variable region sequence selected from the group consisting of amino acids 1-107 of the amino acid sequence of SEQ ID NO: 17 and amino acids 1-110 of the amino acid sequence of SEQ ID NO: 19.
20. The antibody of claim 19, comprising:
- a. a heavy chain variable region sequence comprising amino acids 1-118 of the amino acid sequence of SEQ ID NO: 16 paired with a light chain variable region sequence comprising amino acids 1-107 of the amino acid sequence of SEQ ID NO: 17; or
  - b. a heavy chain variable region sequence comprising amino acids 1-121 of the amino acid sequence of SEQ ID NO: 18 paired with a light chain variable region sequence comprising amino acids 1-110 of the amino acid sequence of SEQ ID NO: 19.
21. A polynucleotide encoding the antibody or antigen binding fragment of any one of claims 1-20.
22. A vector comprising the polynucleotide of claim 21.
23. A host cell comprising the vector of claim 22.
24. A process for the production of an antibody or antigen-binding fragment, comprising: culturing the host cell as defined in claim 23 under the conditions allowing the expression of the antibody or antigen-binding fragment, and recovering the antibody or antigen-binding molecule from the culture.
25. A pharmaceutical composition comprising the antibody, or antigen binding fragment thereof, of any one of claims 1 to 20 and a pharmaceutically acceptable carrier.
26. A kit comprising the antibody, or antigen binding fragment thereof, of any one of claims 1 to 20 and packaging for the same.