

Claims

1. An isolated antibody, or an antigen-binding fragment thereof, wherein the antibody or antigen binding fragment specifically binds to human proTGFβ1 in a complex with human glycoprotein A repetitions predominant (proTGFβ1-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 TGFβ1 growth factor domain,
- a TGFβ2 growth factor domain,
- a TGFβ3 growth factor domain,
- proTGFβ1 covalently associated with LTBP1,
- proTGFβ1 covalently associated with LTBP3,
- proTGFβ1 covalently associated with LRRC33, and
- proTGFβ1 that is unassociated with human GARP,

- a. 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 (IC₅₀) of less than or equal to 10 nM for inhibition of TGFβ1 growth factor release from a cell-associated proTGFβ1-GARP complex under the conditions shown in Example 5, wherein the antibody or antigen binding fragment comprises:
- b. a heavy chain CDR1 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.

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 claim 1, wherein the antibody or antigen binding fragment thereof inhibits the activation of TGFβ1.

4. The antibody or antigen-binding fragment of claim 1, wherein the antibody or antigen binding fragment thereof binds to an epitope of human proTGF β 1 modified as a result of complex formation with human GARP.
5. The antibody or antigen-binding fragment of claim 1, 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 claim 5, wherein the antibody or antigen-binding fragment thereof specifically binds to human proTGF β 1 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 claim 5, wherein the antibody or antigen-binding fragment thereof binds to human proTGF β 1 with a dissociation constant (Kd) of less than or equal to 1 nM for human proTGF β 1 in a complex with human glycoprotein A repetitions predominant (proTGF β 1-GARP complex) under the conditions shown in Example 7 and wherein said proTGF β 1-GARP complex is in solution.
8. An isolated antibody, or an antigen-binding fragment thereof, comprising a heavy chain variable region of the amino acid sequences of SEQ ID NO: 16 and a light chain variable region of the amino acid sequence of SEQ ID NO: 17.
9. The antigen-binding fragment of claim 8 wherein the antigen binding fragment is a Fab fragment, a Fab2 fragment, or a single chain antibody.
10. The antibody or antigen-binding fragment of claim 8 wherein the antibody or antigen-binding fragment is recombinant.
11. The antibody or antigen-binding fragment of claim 10 wherein the antibody or antigen-binding fragment thereof are of IgG1, IgG2, IgG3, or IgG4 isotype.
12. The antibody or antigen-binding fragment of claim 11, wherein the antibody is an IgG4 isotype.

13. An isolated antibody, or an antigen-binding fragment thereof, comprising 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.

14. ~~The~~An isolated antibody, or ~~the~~an antigen-binding fragment thereof, according to claim 13, comprising 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.

15. A polynucleotide encoding the antibody or antigen binding fragment of claim 8.

16. A vector comprising the polynucleotide of claim 15.

17. A host cell comprising the vector of claim 16.

18. A process for the production of an antibody or antigen-binding fragment, comprising: culturing the host cell as defined in claim 17 under the conditions allowing the expression of the antibody or antigen-binding fragment, and recovering the antibody or antigen-binding molecule from the culture.

19. A pharmaceutical composition comprising the antibody, or antigen binding fragment thereof, of claim 8 and a pharmaceutically acceptable carrier.

20. A kit comprising the antibody, or antigen binding fragment thereof, of claim 8 and packaging for the same.