CLAIMS

1. An isolated antibody or antigen-binding portion thereof that binds a pro-protein complex comprising:

i) human proTGFβ1 and

ii) a protein selected from the group consisting of LTBP1, LTBP1S, LTBP2, LTBP3, LTBP4, fibrillin-1, fibrillin-2, fibrillin-3, fibrillin-4, GARP, LRRC33, perlecan, decorin, elastin and collagen,

wherein the antibody or the antigen-binding portion thereof does not bind free mature human TGF-β1, the antibody or the antigen-binding portion thereof does not bind the protein of ii) in its free form, and the antibody or the antigen-binding portion thereof binds the pro-protein complex and prevents mature human TGFβ1 from being released from the pro-protein complex.

2. The antibody or antigen-binding portion according to claim 1, wherein the antibody binds a GARP epitope present in the pro-protein complex.

3. The antibody or antigen-binding portion according to claim 1, wherein the antibody binds an epitope formed by combining regions or portions of two or more of the components selected from the group consisting of:

TGF-β1 growth factor prodomain complex (GPC),

GPC modulatory factor,

growth factor receiving cell,

growth factor receiving receptor,

TGF-β1 LAP,

TGF-β1 fastener region,

TGF-β1 furin cleavage site,

TGF-β1 arm region,

TGF-β1 fingers region,

TGF-β1 LTBP binding domain,

TGF-β1 fibrillin binding domain,

TGF-β1 glycoprotein A repetitions predominant (GARP) binding domain,

TGF-β1 latency lasso,
TGF-β1 alpha 1 region,
TGF-β1 RGD sequence,
TGF-β1 bowtie region,
extracellular matrix, and
cellular matrix.

4. The antibody of claim 1, wherein the antibody binds a combinatorial epitope formed between said GARP and the proTGFβ1.

5. The antibody or antigen-binding portion thereof according to any one of claims 1-4, wherein the GARP has an amino acid sequence selected from the group consisting of: SEQ ID NOs: 158-161.

6. The antibody or antigen-binding portion thereof according to any one of claims 1-5, wherein the antibody or the antigen-binding portion thereof is a human or humanized antibody or an antigen-binding portion thereof.

7. A pharmaceutical composition comprising the antibody or antigen-binding portion thereof according to any one of claims 1-6 and at least one pharmaceutically acceptable excipient.

8. A method for producing an antibody or an antigen-binding fragment thereof that modulates human TGFβ1 growth factor activation, the method comprising steps of:

a) providing an antigen comprising

(i) human proTGFβ1; and,

(ii) a protein selected from the group consisting of LTBP1, LTBP1S, LTBP2, LTBP3, LTBP4, fibrillin-1, fibrillin-2, fibrillin-3, fibrillin-4, GARP, LRRC33, perlecan, decorin, elastin and collagen;

b) selecting for a pool of antibodies or fragments thereof for the ability to bind the antigen of step (a); and,

c) selecting for a pool of antibodies or fragments thereof that inhibits or promotes release of mature human TGFβ1 growth factor from the human proTGFβ1.

9. The method of claim 8, wherein the step (b) precedes step (c), or wherein the step (c) precedes step (b).

10. The method of claim 8 or claim 9, further comprising a step of:

carrying out negative selection, wherein antibodies or fragments thereof that bind a mature human TGFβ1 growth factor are removed from the pool.

11. The method of any one of claims 8-10, further comprising removing antibodies or fragments thereof that bind pro-proteins of related growth factors.

12. The method of any one of claims 8-11, further comprising a step of:

carrying out affinity maturation.

13. The method of any one of claims 8-12, further comprising a step of:

immunizing a host animal with the antigen of step (a).

14. The method of claim 13, further comprising a step of:

collecting lymphocytes from the host animal that bind the antigen of step (a).

15. The method of any one of claims 8-14, wherein step (b) comprises screening a library, optionally wherein the library is:

an antibody display library, or

an antibody fragment display library, optionally com comprising Fab fragments or single-chain variable fragments (scFvs).

16. The method of any one of claims 8-15, further comprising a step of preparing hybridoma cells.

17. The method of any one of claims 8-16, further comprising a step of subjecting the protein complex to proteolytic digestion.

18. An antibody, or antigen-binding fragment thereof, produced by the method of any one of claims 8-17, wherein the antibody or the fragment does not bind a free, mature form of the human TGFβ1 growth factor.

19. Use of the antibody or the fragment according to any one of claims 1-6 or 18 in the manufacture of a medicament for treatment of a TGFβ-related indication; or for modulating an immune response, wound healing, bone growth, endocrine function, or muscle mass.

20. The use of claim 19, wherein the TGFβ-related indication is a fibrotic indication, myelofibrosis, cancer, a cancer-related condition, or a muscle disorder or injury.