CLAIMS

1. A pharmaceutical composition comprising an~~An isolated~~ antibody or antigen-binding ~~portion~~ fragment thereof that binds a pro-protein complex comprising:

i) human proTGFβ31 and

ii) a protein selected from the group consisting of LTBP1, LTBP1S, LTBP2, LTBP3, LTBP4, fibrillin-1, fibrillin-2, fibrillin-3, fibrillin-4, GARP, LRRC3 3, perlecan, decorin, elastin and collagen,

wherein the antibody or the antigen-binding portion thereof does not bind free mature human TGF-β31, the antibody or the antigen-binding ~~portion~~ fragment thereof does not bind the protein of ii) in its free form, and the antibody or the antigen-binding ~~portion~~ fragment thereof ~~binds the pro-protein complex and~~ prevents mature human TGFβ31 from being released from the pro-protein complex, and

at least on pharmaceutically acceptable excipient.

2. The pharmaceutical composition according to claims 1, wherein the antibody, or the antigen-binding fragment thereof, beings TGFβ1 latency lasso.

3. The ~~antibody or antigen-binding portion~~ pharmaceutical composition according to claim 1, wherein the antibody, or the antigen-binding fragment thereof, binds a GARP epitope present in the pro-protein complex.

~~3~~4. The ~~antibody or antigen-binding portion~~pharmaceutical composition according to claim 1, wherein the antibody, or the antigen-binding fragment thereof, binds an epitope formed by combining regions or ~~portions~~ fragments 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.

45. The ~~antibody~~ pharmaceutical composition ~~of~~ according to claim 1, wherein the antibody, or the antigen-binding fragment thereof, binds a combinatorial epitope formed between said GARP and the proTGFβ1.

56. The ~~antibody or antigen-binding portion thereof~~ pharmaceutical composition according to any one of claims 1-45, wherein the GARP has an amino acid sequence selected from the group consisting of: SEQ ID NOs: 158-161.

67. The ~~antibody or antigen-binding portion thereof~~ pharmaceutical composition according to any one of claims 1-56, wherein the antibody or the antigen-binding ~~portion~~ fragment thereof is a human or humanized antibody or an antigen-binding ~~portion~~ fragment 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 optionally,

(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), wherein optionally the antigen is a cell-based antigen.

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~~ antigen 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. The antibody or antigen-binding fragment of claim 18, wherein the antibody, or fragment thereof, binds the TGFβ latency lasso.

~~19~~20. Use of the antibody, or the antigen-binding fragment according to ~~any one of claims 1-6~~ claim 18 or ~~18~~ 19 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~~21. The use of claim ~~19~~20, wherein the TGFβ-related indication is a fibrotic indication, myelofibrosis, cancer, a cancer-related condition, or a muscle disorder or injury.

22. The use of claim 21, wherein the TGFβ-related indication is myelofibrosis or cancer, and wherein the antibody or the antigen-binding fragment is to be used in combination with a cancer immunotherapy, radiotherapy and/or chemotherapy.

23. The use of claim 22, wherein the antibody or the antigen-binding fragment is to be used in combination with a cancer immunotherapy.

24. The use of claim 22, wherein the antibody or the antigen-binding fragment is to be used in combination with radiotherapy.

25. The use of claim 22, wherein the antibody or the antigen-binding fragment is to be used in combination with chemotherapy.

26. A method of treating a TGFβ-related indication, comprising administering the pharmaceutical composition of any one of claims 1-7 and a cancer immunotherapy, chemotherapy and/or radiotherapy to a subject, wherein the TGFβ-related indication is myelofibrosis or cancer.

27. The method of claim 26, wherein the pharmaceutical composition is used in combination with a cancer immunotherapy.

28. The method of claim 26, wherein the pharmaceutical composition is used in combination with radiotherapy.

29. The method of claim 26, wherein the pharmaceutical composition is used in combination with chemotherapy.

30. Use of the pharmaceutical composition of any one of claims 1-7 in the manufacture of a medicament for treatment of a TGFβ-related indication, wherein the pharmaceutical composition is to be used in combination with a cancer immunotherapy, radiotherapy and/or chemotherapy, and wherein the TGFβ-related indication is myelofibrosis or cancer.

31. The method of claim 30, wherein the pharmaceutical composition is used in combination with a cancer immunotherapy.

32. The method of claim 30, wherein the pharmaceutical composition is used in combination with radiotherapy.

33. The method of claim 30, wherein the pharmaceutical composition is used in combination with chemotherapy.