

CLAIMS

1. ~~1. A composition for use in a method for treating a disease associated with TGF β 1 dysregulation in a human subject,~~

~~wherein the composition comprises an isoform-specific inhibitor of TGF β 1 and a pharmaceutically acceptable excipient,~~

~~wherein the inhibitor targets both ECM-associated TGF β 1 and immune cell-associated TGF β 1 but does not target TGF β 2 or TGF β 3 in vivo, wherein optionally the inhibitor inhibits the activation step of TGF β 1; and,~~

~~wherein the disease is characterized by dysregulation or impairment at least two of the following attributes:~~

~~a) regulatory T cells (Treg);~~

~~b) effector T cell (Teff) proliferation or function;~~

~~c) myeloid cell proliferation or differentiation;~~

~~d) monocyte recruitment or differentiation;~~

~~e) macrophage function;~~

~~f) epithelial to mesenchymal transition (EMT) and/or endothelial to mesenchymal transition (EndMT);~~

~~g) gene expression in one or more of marker genes selected from the group consisting of: PAI-1, ACTA2, CCL2, Col1a1, Col3a1, FN-1, CTGF, and TGF β 1;~~

~~h) ECM components or function;~~

~~i) fibroblast differentiation; and,~~

~~wherein the method comprises administration of a therapeutically effective amount of the composition to the human subject who is diagnosed with the disease.~~

2. The composition for use according to claim 1, wherein the ECM-associated TGF β 1 is LTBP1-presented TGF β 1 and/or LTBP3-presented TGF β 1; and, wherein the immune cell-associated TGF β 1 is GARP-presented TGF β 1 and/or LRRRC33-presented TGF β 1.

3. The composition for use according to claim 1 or 2, wherein the human subject suffers from a disease involving a proliferative component and/or a fibrotic component.

4. The composition for use according to claim 3, wherein the disease is a cancer, wherein optionally the cancer is a metastatic cancer.

5. The composition for use according to claim 4, wherein the cancer comprises a solid tumor that is TGF β 1-positive, wherein optionally the solid tumor is a desmoplastic tumor.

~~6. The composition for use according to claim 4, wherein the cancer is a myeloproliferative disorder, wherein optionally, the myeloproliferative disorder is essential thrombocythemia (ET), polycythemia vera (PV) or primary myelofibrosis (PMF).~~

~~7. The composition for use according to claim 4, wherein the cancer is associated with an increased number of Tregs, TAMs, TANs, MDSCs, CAFs, or any combinations thereof.~~

~~8. The composition for use according to claim 4, wherein the cancer is poorly responsive to a cancer therapy selected from the group consisting of: radiation therapy, chemotherapy and checkpoint inhibitor therapy, wherein the checkpoint inhibitor therapy optionally comprises a PD-1 antagonist, PD-L1 antagonist or CTLA-4 antagonist; wherein further optionally the poor response is due to intrinsic resistance or acquired resistance.~~

~~9. The composition for use according to claim 8, wherein the subject has an immune checkpoint inhibitor resistant cancer selected from the group consisting of:~~

~~Myelofibrosis, melanoma, renal cell carcinoma, bladder cancer, colon cancer, hematologic malignancies, non-small cell carcinoma, non-small cell lung cancer (NSCLC), lymphoma (classical Hodgkin's and non-Hodgkin's), head and neck cancer, urothelial cancer, microsatellite instability-high cancer, mismatch repair deficient cancer, gastric cancer, renal cancer, and hepatocellular cancer.~~

~~10. The composition for use according to claim 8, wherein a clinical sample of the human subject shows expression of GARP and/or LRRC33; and/or, wherein TGF β 1 expression in the clinical sample is greater than TGF β 2 or TGF β 3 expression, wherein optionally the expression is determined by RNA levels and/or protein levels.~~

~~11. The composition for use according to any one of claims 4-10, wherein the therapeutically effective amount is an amount effective to achieve one or more of the following clinical effects:~~

- ~~a) reduced tumor growth;~~
- ~~b) reduced metastasis;~~
- ~~c) reduced tumor invasion;~~
- ~~d) reduced angiogenesis and vascularization/vascularity;~~
- ~~e) reduced monocyte recruitment to a tumor site;~~
- ~~f) reduced TAM infiltration of the tumor;~~
- ~~g) reduced macrophage activation;~~
- ~~h) increased ratios of M1 to M2 (TAM-like) macrophage populations at a tumor site;~~
- ~~i) reduced number of CAFs at a tumor site;~~
- ~~j) reduced immuno-suppression;~~
- ~~k) enhanced responsiveness to a cancer therapy;~~
- ~~l) prolonged survival;~~
- ~~m) prolonged refractory period;~~

~~—— n) increased rates of complete remission or complete responses;~~
~~—— o) decreased ratios of Treg/Teff cells at a tumor site;~~
~~—— p) increased number of Teff cells at a tumor site;~~
~~—— q) reduced number of Treg cells at a tumor site;~~
~~—— r) reduced number of MDSCs and/or TANs in the subject; and,~~
~~—— wherein the clinical effect(s) is/are achieved with an acceptable level of toxicities in the subject.~~

~~12. — The composition for use according to claim 4, 6, 8-10, wherein the therapeutically effective amount is an amount effective to achieve at least two of the following clinical benefits:~~

- ~~a) reduced fibrosis in a bone marrow;~~
- ~~b) enhanced hematopoiesis of differentiated blood cells in a bone marrow;~~
- ~~c) reduced proliferation of abnormal stem cells in the bone marrow, wherein optionally the abnormal stem cells are CD133-positive;~~
- ~~d) reduced megakaryocytes in a bone marrow and/or spleen;~~
- ~~e) reduced occurrence and/or extent of extramedullary hematopoiesis in the subject, wherein optionally the extramedullary hematopoiesis is in spleen;~~
- ~~f) reduced need for bone marrow transplantation;~~
- ~~g) prolonged survival;~~
- ~~h) normalized levels of one or more of expression markers, wherein the expression marker optionally is selected from the group consisting of BMP1, BMP6, BMP7, and BMP-receptor 2, PLOD2, TGFβ1, bFGF, platelet-derived growth factor (PDGF), Col1, metalloproteinases, FN1, CXCL12, VEGF, CXCR4, IL-2, IL-3, IL-9, CXCL1, IL-5, IL-12, TNFα, Bmp2, Bmp5, Acvrl1, Tgfbll1, Igf1, Cdkn1a, Ltbp1, Gdf2, Lefty1 and Nodal; and,~~
- ~~i) reduced chronic inflammation in the bone marrow.~~

~~13. — The composition for use according to claim 3, wherein the human subject has an organ fibrosis, wherein optionally the organ fibrosis is liver fibrosis, lung fibrosis, kidney fibrosis, skin fibrosis and/or cardiac fibrosis.~~

~~14. — The composition for use according to claim 13, wherein the subject has an organ fibrosis and is not a candidate for organ transplantation.~~

~~15. — The composition for use according to any one of claims 3, 13 and 14, wherein the subject has a fibrotic disorder with chronic inflammation.~~

~~16. — The composition for use according to claim 15, wherein the fibrotic disorder is a muscular dystrophy, wherein optionally the muscular dystrophy is DMD.~~

17. ~~The composition for use according to any one of the preceding claims, wherein the isoform-selective inhibitor inhibits three or more of the following TGF β 1 activities:~~

- ~~a) GARP-mediated TGF β 1 activity;~~
- ~~b) LRRC33-mediated TGF β 1 activity;~~
- ~~c) LTBP1-mediated TGF β 1 activity, and~~
- ~~d) LTBP3-mediated TGF β 1 activity;~~

~~wherein optionally the inhibitor inhibits all of the TGF β 1 activities (a)-(d).~~

18. ~~The composition according to any one of the preceding claims, wherein the inhibitor is a monoclonal antibody or fragment thereof.~~

19. ~~The composition for use according to claim 18, wherein the monoclonal antibody or fragment thereof binds a protein complex comprising a pro/latent TGF β 1, wherein optionally the protein complex further comprises a presenting molecule selected from the group consisting of: LTBP1, LTBP3, GARP and LRRC33.~~

20. ~~The composition of claim 18 or 19, wherein the antibody or fragment thereof specifically binds an epitope within pro/latent TGF β 1, wherein optionally the epitope is within a prodomain of the pro/latent TGF β 1.~~

21. ~~The composition of claim 18-20, wherein the antibody or fragment thereof specifically binds a combinatorial epitope and/or a conformational epitope.~~

22. ~~The composition of claim 18-21, wherein the monoclonal antibody inhibits release of mature TGF β 1 growth factor from a latent protein complex comprising pro/latent TGF β 1.~~

23. ~~The composition for use according to claim 18-22, wherein the antibody or the fragment thereof is a fully human or humanized antibody.~~

24. ~~The composition for use according to claim 18-23, wherein the antibody is a human IgG₄ antibody, wherein optionally the human IgG₄ antibody comprises a backbone substitution.~~

25. ~~The composition for use according to claim 18-24, wherein the antibody has the following CDR sequences, optionally with three or fewer substitutions:~~

- ~~CDR-H1: NYAMS (SEQ ID NO: 85);~~
- ~~CDR-H2: SISGSGGATYYADSVKG (SEQ ID NO: 86);~~
- ~~CDR-H3: ARVSSGHWDFDY (SEQ ID NO: 87);~~
- ~~CDR-L1: RASQSISSYLN (SEQ ID NO: 88);~~
- ~~CDR-L2: SSLQS (SEQ ID NO: 89); and,~~
- ~~CDR-L3: QQSYAPFT (SEQ ID NO: 90).~~

~~261. A pharmaceutical composition comprising an~~ An antibody comprising a heavy chain variable region polypeptide that is at least 90% identical to an amino acid sequence set forth in SEQ ID NO:95, and, a light chain variable region polypeptide that is at least 90% identical to an amino acid sequence set forth in SEQ ID NO:97, wherein the antibody binds and inhibits release of mature TGFβ1 growth factor from a protein complex comprising a pro/latent TGFβ1, and wherein the antibody comprises the following CDR-L1 sequence: RASQSISSYLN (SEQ ID NO: 88).

~~27. A pharmaceutical composition comprising an antibody having the following CDR sequences optionally with three or fewer substitutions:~~

~~CDR-H1: NYAMS (SEQ ID NO: 85);~~

~~CDR-H2: SISGSGGATYYADSVKG (SEQ ID NO: 86);~~

~~CDR-H3: ARVSSGHWDFDY (SEQ ID NO: 87);~~

~~CDR-L1: RASQSISSYLN (SEQ ID NO: 88);~~

~~CDR-L2: SSLQS (SEQ ID NO: 89); and,~~

~~CDR-L3: QQSYSAPFT (SEQ ID NO: 90).~~

~~28. The pharmaceutical composition according to claim 27, wherein the antibody has the CDR sequences with no substitutions.~~

2. The antibody of claim 1, wherein the heavy chain variable region polypeptide is at least 95% identical to an amino acid sequence set forth in SEQ ID NO:95, and, the light chain variable region polypeptide is at least 95% identical to an amino acid sequence set forth in SEQ ID NO:97.

3. The antibody according to claim 1, comprising a heavy chain variable region polypeptide comprising an amino acid sequence set forth in SEQ ID NO:95, and a light chain variable region polypeptide comprising an amino acid sequence set forth in SEQ ID NO:97.

4. The antibody of claim 3, comprising a heavy chain variable region polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:95, and a light chain variable region polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:97.

5. The antibody of claim 1, wherein the antibody comprises a heavy chain polypeptide comprising an amino acid sequence set forth in SEQ ID NO:99, and a light chain polypeptide comprising an amino acid sequence set forth in SEQ ID NO:100.

6. The antibody of claim 5, wherein the antibody comprises a heavy chain polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:99, and a light chain polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:100.

7. The antibody of any one of claims 1-6, wherein the antibody is a monoclonal antibody.

8. The antibody of any one of claims 1-7, wherein the antibody is a fully human antibody or humanized antibody.

9. The antibody of any one of claims 1-8, wherein the antibody is a human IgG₄ antibody, wherein optionally the human IgG₄ antibody comprises a backbone substitution.

10. The antibody of any one of claims 1-9, wherein the antibody binds a protein complex comprising a pro/latent TGFβ₁, wherein the protein complex further comprises a presenting molecule selected from the group consisting of: LTBP1, LTBP3, GARP and LRRC33.

11. A pharmaceutical composition comprising an antibody of any one of claims 1-10.

12. The pharmaceutical composition according to claim 11, further comprising at least one additional therapeutic agent.

13. Use of the antibody of any one of claims 1-10, or the pharmaceutical composition of claim 11 or claim 12 in the preparation of a medicament for treating a fibrotic indication or condition in a human subject in need of such treatment.

14. The use according to claim 13, wherein the fibrotic indication or condition is selected from the group consisting of idiopathic pulmonary fibrosis (IPF); chronic obstructive pulmonary disorder (COPD); allergic asthma; acute lung injury; eosinophilic esophagitis; pulmonary arterial hypertension; diabetic glomerulosclerosis; focal segmental glomeruloclerosis (FSGS); chronic kidney disease (CKD); fibrosis associated with kidney transplantation and chronic rejection, IgA nephropathy, and hemolytic uremic syndrome; non-alcoholic steatohepatitis (NASH); chronic viral hepatitis; parasitemia; alcohol fibrosis; non-alcoholic steatohepatitis-hepatocellular carcinoma (NASH-HCC); primary biliary cirrhosis; sclerosing cholangitis; cardiovascular fibrosis; systemic sclerosis, diffuse cutaneous systemic sclerosis; scleroderma, pathological skin scarring; keloid; postsurgical scarring; scar revision surgery; and radiation-induced scarring.

15. The use according to claim 13, wherein the fibrotic indication or condition is selected from the group consisting of IPF, COPD, pulmonary arterial hypertension, CKD, NASH, NASH-HCC, primary biliary cirrhosis and systemic sclerosis.

16. The use according to claim 13, wherein the human subject has an organ fibrosis, wherein optionally the organ fibrosis is liver fibrosis, lung fibrosis, kidney fibrosis, skin fibrosis and/or cardiac fibrosis,

wherein further optionally the subject has an organ fibrosis and is not a candidate for organ transplantation.

17. The use according to claim 16, wherein the subject has a fibrotic disorder with chronic inflammation.

18. The use according to claim 17, wherein the fibrotic disorder a muscular dystrophy, wherein optionally the muscular dystrophy is DMD.

19. The use according to any one of claims 13 to 18, wherein the antibody is used in combination with at least one additional therapeutic agent.

20. The use according to claim 19, wherein the additional therapeutic agent comprises a myostatin inhibitor, a VEGF agonist, an IGF1 agonist, an FXR agonist, a CCR2 inhibitor, a CCR5 inhibitor, a dual CCR2/CCR5 inhibitor, a lysyl oxidase-like-2 inhibitor, an ASK1 inhibitor, an Acetyl-CoA Carboxylase (ACC) inhibitor, a p38 kinase inhibitor, Pirfenidone, Nintedanib, a GDF11 inhibitor, or a JAK inhibitor.

21. The use according to claim 19, wherein the additional therapeutic agent comprises an ASK1 inhibitor, an FXR agonist, or an ACC inhibitor.

22. The pharmaceutical composition according to claim 12, wherein the additional therapeutic agent comprises a myostatin inhibitor, a VEGF agonist, an IGF1 agonist, an FXR agonist, a CCR2 inhibitor, a CCR5 inhibitor, a dual CCR2/CCR5 inhibitor, a lysyl oxidase-like-2 inhibitor, an ASK1 inhibitor, an Acetyl-CoA Carboxylase (ACC) inhibitor, a p38 kinase inhibitor, Pirfenidone, Nintedanib, a GDF11 inhibitor, or a JAK inhibitor.

23. The pharmaceutical composition according to claim 12, wherein the additional therapeutic agent comprises an ASK1 inhibitor, an FXR agonist, or an ACC inhibitor.

24. A nucleic acid encoding an antibody of any one of claims 1-10.