

CLAIMS

1. Use of an isoform-specific inhibitor of TGF β 1 in the manufacture of a medicament for the treatment of cancer or myelofibrosis, wherein the isoform-specific inhibitor is:

(a) an antibody or an antigen-binding fragment thereof which comprises a heavy chain variable region comprising a CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising a CDRL1, CDRL2, and CDRL3, wherein:

CDRH1 comprises a sequence as set forth in SEQ ID NO: 2;

CDRH2 comprises a sequence as set forth in SEQ ID NO: 4;

CDRH3 comprises a sequence as set forth in SEQ ID NO: 6;

CDRL1 comprises a sequence as set forth in SEQ ID NO: 8;

CDRL2, comprises a sequence as set forth in SEQ ID NO: 10; and

CDRL3 comprises a sequence as set forth in SEQ ID NO: 12;

(b) an antibody or an antigen-binding fragment thereof which comprises a heavy chain variable region comprising a CDRH1, CDRH2, and CDRH3 and a light chain variable region comprising a CDRL1, CDRL2, and CDRL3, wherein:

CDRH1 comprises a sequence as set forth in SEQ ID NO: 1;

CDRH2 comprises a sequence as set forth in SEQ ID NO: 3;

CDRH3 comprises a sequence as set forth in SEQ ID NO: 5;

CDRL1 comprises a sequence as set forth in SEQ ID NO: 7;

CDRL2, comprises a sequence as set forth in SEQ ID NO: 9; and

CDRL3 comprises a sequence as set forth in SEQ ID NO: 11; or

(c) an antibody or an antigen-binding fragment thereof which competes or cross-competes with the antibody defined in part (a) or (b) for binding to TGF β 1;

wherein, a therapeutically effective dose of the inhibitor does not cause a cardiovascular toxicity associated with TGF β inhibition in a subject,

wherein the antibody or the antigen-binding fragment thereof specifically binds a pro/latent TGF β 1 complex, which comprises LTBP1, LTBP3, GARP or LRRC33; and

wherein the antibody or antigen-binding fragment thereof does not bind TGF β 2 or TGF β 3.

2. The use according to claim 1, wherein the antibody or the antigen-binding fragment of part (a) comprises a heavy chain variable region comprising a sequence as set forth in SEQ ID NO: 17 and a light chain variable region comprising a sequence as set forth in SEQ ID NO: 18 or wherein the antibody or antigen-binding fragment of part (b) comprises a heavy chain variable region comprising a sequence as set forth in SEQ ID NO: 13 and a light chain variable region comprising a sequence as set forth in SEQ ID NO: 14.

3. The use according to claim 1 or claim 2, wherein the cancer is a cancer or tumor found in the colon, anus, bladder, bile duct, bone, brain, breast, cervix, rectum, endometrium, esophagus, eye, gallbladder, head and neck, liver, kidney, larynx, lung, mediastinum (chest), mouth, ovaries, pancreas, penis, prostate, skin, small intestine, stomach, spinal marrow, tailbone, testicles, thyroid or uterus.
4. The use according to claim 1, wherein the cardiovascular toxicity comprises heart valve lesions, wherein optionally the heart valve lesions include hemorrhage, inflammation, degeneration and/or proliferation of valvular interstitial cells.
5. The use according to claim 4, wherein the cardiovascular toxicities include valvulopathy.
6. The use according to any one of claims 1-5, wherein the inhibitor reduces tumor growth.
7. The use according to any one of claims 1-6, wherein the inhibitor reduces the suppressive activity of regulatory T cells.
8. The use according to any one of claims 1-7, wherein the antibody or antigen-binding fragment thereof inhibits the release of mature TGF β 1 from the GARP-TGF β 1 complex, the LTBP1-TGF β 1 complex, the LTBP3-TGF β 1 complex, and/or the LRRC33-TGF β 1 complex.
9. The use according to any one of claims 1-8, wherein the therapeutically effective dose of from about 0.1 μ g/kg to about 30 mg/kg.
10. The use according to any one of claims 1-9, wherein the inhibitor inhibits or decreases solid tumor growth.
11. The use according to any one of claims 1-10, further comprising an additional agent or therapy.
12. The use according to claim 11, wherein the additional agent is a checkpoint inhibitor.
13. The use according to claim 12, wherein the checkpoint inhibitor is selected from the group consisting of an anti-PD1 antibody, a PD-1 antagonist, a PDL1 antagonist, or a PD-L1 or PDL2 fusion protein, a CTLA4 antagonist, a GITR agonist, an anti-ICOS antibody, an anti-ICOSL antibody, an anti-B7H3 antibody, an anti-B7H4 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, an anti-OX40 antibody, an anti-CD27 antibody, an anti-CD70 antibody, an anti-CD47 antibody, an anti-41BB antibody, an oncolytic virus, and a PARP inhibitor.

14. Use of an effective amount of a combination of an isoform-specific inhibitor of TGF β 1 and a checkpoint inhibitor in the manufacture of a medicament for the treatment of cancer,
wherein the isoform-specific inhibitor of TGF β 1 is an antibody, or an antigen binding fragment thereof; wherein the antibody, or the antigen-binding fragment thereof, specifically binds a pro/latent TGF β 1 complex, which comprises LTBP1, LTBP3, GARP or LRRC33, and does not bind TGF β 2 or TGF β 3; and
wherein the checkpoint inhibitor is a PD-1 antagonist or PD-L1 antagonist; and wherein the combination produces a synergistic effect in the treatment of the cancer.
15. Use of an effective amount of a combination of an isoform-specific inhibitor of TGF β 1 and a checkpoint inhibitor in the manufacture of a medicament for reducing tumor growth in a subject, wherein the isoform-specific inhibitor of TGF β 1 is an antibody, or an antigen binding fragment thereof; wherein the antibody, or the antigen-binding fragment thereof, specifically binds a pro/latent TGF β 1 complex, which comprises LTBP1, LTBP3, GARP or LRRC33, and does not bind TGF β 2 or TGF β 3; and wherein the checkpoint inhibitor is a PD-1 antagonist or PD-L1 antagonist.
16. The use according to claim 15 or claim 16, wherein the isoform-specific inhibitor of TGF β 1 and the checkpoint inhibitor are formulated as a single formulation or as separate formulations.
17. The use according to any one of claims 14-16, wherein the checkpoint inhibitor is a PD-1 antibody.
18. The use according to any one of claims 14-17, wherein the cancer or tumor is a solid tumor.
19. A method for selecting an antibody or an antigen-binding fragment thereof which is an isoform specific inhibitor of TGF β 1 for use as medicament, the method comprising the steps of:
i) providing one or more antibodies or an antigen-binding fragments that inhibit signaling of at least one isoform of TGF β ;
ii) measuring activities of the one or more antibodies or an antigen-binding fragments towards all isoforms of TGF β ;
iii) selecting an antibody or an antigen-binding fragment for specific activity against the activation of TGF β 1 isoform, wherein the selected antibody or the antigen-binding fragment specifically binds and blocks activation of TGF β 1, but not TGF β 2 or TGF β 3;
iv) formulating into a pharmaceutical composition the isoform-specific inhibitor of TGF β 1 activation selected in step iii) and a pharmaceutically acceptable excipient;
wherein the antibody or antigen-binding fragment specifically binds a pro/latent complex of TGF β 1 comprising GARP, LRRC33, LTBP1, and/or LTBP3.

20. A method for selecting an isoform-specific TGF β 1 inhibitor for use as a medicament, the method comprising the steps of:
- i) selecting an isoform-specific TGF β 1 inhibitor;
 - ii) carrying out an *in vivo* efficacy study to assess therapeutic effectiveness of the isoform-specific TGF β 1 inhibitor in an animal model;
 - iii) carrying out an *in vivo* safety study to assess toxicities of the isoform-specific TGF β 1 inhibitor in an animal model, wherein the *in vivo* safety study comprises evaluation of adverse effects selected from the group consisting of: cardiovascular toxicities, gastrointestinal toxicities, immune toxicities, bone/cartilage toxicities, reproductive toxicities, and renal toxicities;
- wherein, a dosage found to be therapeutically effective in step (ii) is within a dosage found to achieve safety determined in step (iii); and,
- formulating into a pharmaceutical composition comprising the isoform-specific TGF β 1 inhibitor and a pharmaceutically acceptable excipient.
21. The method of claim 20, wherein the inhibitor specifically binds a pro/latent complex of TGF β 1 but does not bind free mature TGF β 1 which is not associated with a pro/latent complex comprising GARP, LRRC33, LTBP1, and/or LTBP3.
22. A pharmaceutical composition produced by the method of any one of claims 19-21.