the present disclosure have identified a class of high-affinity monoclonal antibodies and fragments thereof, capable of specifically targeting proTGFβ1 complexes and potently blocking TGFβ1 activation. In some embodiments, the novel antibodies disclosed herein show high affinities across all target LLCs (e.g., KD of nanomolar to sub-nanomolar range). In preferred embodiments, such antibody is unbiased across different proTGFβ1 complexes such that the antibody has equivalent affinities for all target complexes. Related compositions, therapeutic use, preparations, formulations, processes, and methods are encompassed by the invention.

[12a] In some embodiments, the invention includes an antibody or an antigen-binding fragment thereof that binds each of the following antigen complexes with a KD of ≤ 5 nM, as measured by biolayer interferometry: i) human LTBP1-proTGFβ1; ii) human LTBP3-proTGFβ1; iii) human GARP-proTGFβ1; and, iv) human LRRC33-proTGFβ1; wherein the antibody or the fragment thereof inhibits TGFβ1 activation; wherein the antibody or the fragment thereof is a fully human or humanized antibody or fragment thereof; wherein the antibody or the fragment thereof comprises: an H-CDR1 represented by the formula FTF(X_1)(X_2)(X_3)(X_4)M(X_5), wherein: X_1 is S, G or A; X_2 is S or F; X_3 is F or Y; X_4 is S or A; and X_5 is D, N or Y (SEQ ID NO: 143); an H-CDR2 represented by the formula YI(X_1)(X_2)(X_3)A(X_4)TIYYA(X_5)SVKG, wherein: X_1 is S or H; X_2 is P or S; X_3 is S or D; X_4 is D or S; and X_5 is D or G (SEQ ID NO: 144); an H-CDR3 represented by the formula (X_1)R(X_2)(X_3)(X_4)D(X_5)GDML(X_6)P, wherein: X_1 is A or V; X_2 is G or A; X_3 is V or T; X_4 is L or W; X_5 is Y or M; and X_6 is M or D (SEQ ID NO: 145); an L-CDR1 set forth in SEQ ID NO: 105; an L-CDR2 set forth in SEQ ID NO: 106; and an L-CDR3 set forth in SEQ ID NO: 12.

[12b] In some embodiments, the invention includes an antibody or an antigen-binding fragment thereof that binds each of the following antigen complexes with a KD of ≤ 0.5 nM, as measured by biolayer interferometry: i) human LTBP1-proTGFβ1; ii) human LTBP3-proTGFβ1; iii) human GARP-proTGFβ1; and, iv) human LRRC33-proTGFβ1; wherein the antibody or the fragment thereof inhibits TGFβ1 activation; wherein the antibody or the fragment thereof is a fully human or humanized antibody or fragment thereof; wherein the antibody or the fragment thereof comprises a heavy chain variable domain (VH) having at least 90% sequence identity to SEQ ID NO: 13 and a light chain variable domain (VL) having at least 90% sequence identity to SEQ ID NO: 15.

[12c] In some embodiments, the invention includes a composition comprising the antibody, or the antigen-binding fragment thereof, of any one of the preceding claims, and an excipient.

[12d] In some embodiments, the invention includes a use of the antibody or the antigen-binding fragment thereof as described herein, or the composition as described herein in the manufacture of a medicament for treating a proliferative and/or fibrotic disorder in a subject.

[12e] In some embodiments, the invention includes a method for manufacturing a pharmaceutical composition comprising: i) providing an antibody or antigen-binding fragment thereof according to any one of claims 1-8; ii) formulating the antibody or the antigen-binding fragment thereof into a pharmaceutical composition with a pharmaceutically acceptable carrier.

[12f] In some embodiments, the invention includes the antibody or the antigen-binding fragment thereof as described herein, or the composition as described herein for use in therapy.

[13] Accordingly, in some embodiments, the invention includes a monoclonal antibody or antigen-binding fragment thereof that is capable of binding to each of the following human LLC complexes with a KD of ≤ 10 nM, as measured by solution equilibrium titration: LTBP1-proTGFβ1, LTBP3-proTGFβ1, GARP-proTGFβ1 and LRRC33-proTGFβ1. In some embodiments, the antibody binds each of the human LTBP1-proTGFβ1 and LTBP3-proTGFβ1 complexes with a KD of ≤ 1 nM. Preferably, the antibody has a KD of ≤ 1 nM for each of the four human LLCs.

[14] In some embodiments, the antibody or the fragment binds Latency Lasso, or a portion thereof, of proTGFβ1. In some embodiments, the antibody or the fragment further binds a portion(s) of the growth factor domain, such as Finger-1 and Finger-2. For example, the antibody or the fragment may bind an epitope comprising one or more amino acid residues of Latency Lasso. Optionally, the epitope may further comprise one or more amino acid residues of the growth factor domain. Such epitope therefore may be a combinatorial epitope. In preferred embodiments, the antibody does not bind free TGFβ1 growth factor which is not in association with a proTGFβ1 complex.

[15] The TGFβ1 inhibitors of the invention are functional antibodies in that they have inhibitory activities towards TGFβ1. The potency of such antibodies is isoform-specific, as measured by suitable in vitro potency assays such as cell-based reporter assays described herein. Thus, the antibody does not bind or inhibit TGFβ2 or TGFβ3 counterparts.

[16] The TGFβ1 inhibitors of the invention are capable of blocking the release of mature growth factor from latent LLC complexes. In some embodiments, the TGFβ1 inhibitors can inhibit integrin-dependent activation of TGFβ1 and/or protease-dependent activation of TGFβ1. In some embodiments, the protease is Kallikrein, Plasmin, or an MMP protease. In some embodiments, the TGFβ1 inhibitors block integring-dependent TGFβ1 activation without blocking integrin binding to the LLCs.

[17] In some embodiments, the TGFβ1 inhibitors of the invention may function through dual inhibitory modes of action towards cell-associated LLCs (e.g., GARP-proTGFβ1 and LRRC33-proTGFβ1). In one mechanism, such inhibitors block the activation step of TGFβ1 associated with the membrane-anchored GARP and/or LRRC33. In a second mechanism, such inhibitors may, upon target engagement, induce antibody-dependent internalization (hence removal) of the LLCs from cell surface, thereby reducing TGFβ1 signaling at the niche. In some embodiments, the antibody is a pH-seneitive antibody characterized in that the antibody binds to a proTGFβ1 complex with higher affinity in a neutral pH than in an acidic pH.

[18] In some embodiments, the TGFβ1 inhibitors of the invention are effective to reduce expression of disease-associated genes, such as TGFB1, Acta2, Col1a1, Col3a1, Fn1, Itga11, Lox, Loxl2, CCL2 and Mmp2.

[19] In some embodiments, the TGFβ1 inhibitors of the invention are effective to reduce phosphorylation of the downstream effector SMAD2/3 in vivo.

[20] In some embodiments, the TGFβ1 inhibitors of the invention are effective to treat TGFβ1-related indications. Such indications include diseases involving abnormal gene expression, diseases involving ECM dysregulation, diseases characterized by increased immunosuppressive cells (e.g., Tregs, MDSCs and/or M2 macrophages), diseases involving mesenchymal transition, diseases involving proteases, diseases related to abnormal stem cell