LTBP COMPLEX-SPECIFIC INHIBITORS OF TGFβ AND USES THEREOF

RELATED APPLICATIONS

[001] This international application claims the benefit of and priority to U.S. Provisional Application No. 62/798,927, filed January 30, 2019, the contents of which are expressly incorporated herein by reference in entirety.

SEQUENCE LISTING

[001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 13, 2020, is named 127036-03020_SL.txt and is 376,831 bytes in size.

BACKGROUND

[002] Transforming growth factor beta (TGFβ) superfamily of growth factors are involved in a number of signaling cascades that regulate diverse biological processes including, but not limited to: inhibition of cell growth, tissue homeostasis, extracellular matrix (ECM) remodeling, endothelial to mesenchymal transition, cell migration and invasion, and immune modulation/suppression, as well as mesenchymal to epithelial transition. In relation to ECM remodeling, TGFβ signaling may increase fibroblast populations and ECM deposition (*e.g.,* collagen). In the immune system, TGFβ ligand modulates T regulatory cell function and maintenance of immune precursor cell growth and homeostasis. In normal epithelial cells, TGFβ is a potent growth inhibitor and promoter of cellular differentiation. However, as tumors develop and progress, they frequently lose their negative growth response to TGFβ. In this setting, TGFβ may become a promoter of tumor development due to its ability to stimulate angiogenesis, alter the stromal environment, and induce local and systemic immunosuppression. For these and other reasons, TGFβ has been a therapeutic target for a number of clinical indications. Despite much effort made to date by a number of groups, clinical development of a TGFβ therapeutic has been challenging.

[003] Observations from preclinical studies, including in rats and dogs, have revealed certain toxicities associated with inhibition of TGFβ *in vivo*. Moreover, although several TGFβ inhibitors have been developed to date, most clinical programs targeting TGFβ have been discontinued due to side effects or risk of toxicity.

[004] For example, Anderton *et al.* (Toxicology Pathology, 39: 916-24, 2011) reported that small molecule inhibitors of TGFβ type I (ALK5) receptor induced heart valve lesions characterized by hemorrhage, inflammation, degeneration and proliferation of valvular interstitial cells in a preclinical animal model. The toxicity was observed in all heart valves at all doses tested. Frazier *et al.* (Toxicology Pathology, 35: 284-295, 2007) reported that administration of the small molecule inhibitor of TGFβ type I (ALK5) receptor GW788388 induced physeal dysplasia in rats.

[005] Stauber *et al.* (J. Clin. Practice 4:3, 2014) reported that a chronic (≥ 3 months) administration of the inhibitor of TGFβ receptor I kinase, LY2157299, which is being investigated for certain cancer

treatments, caused multiple organ toxicities involving the cardiovascular, gastrointestinal, immune, bone/cartilage, reproductive, and renal systems, in rats and dogs.

[006] Fresolimumab (GC1008), a "pan" TGFβ antibody capable of neutralizing all human isoforms of TGFβ, has been reported to induce an epithelial hyperplasia of the gingiva, bladder, and of the nasal turbinate epithelium after multiple administrations in studies with cynomolgus macaques (Lonning *et al.*, Current Pharmaceutical Biotechnology 12: 2176-89, 2011). Similarly, a variety of skin rashes/lesions, gingival bleeding and fatigue have been reported in clinical trials after administration of multiple doses of the drug. The most notable adverse reaction to fresolimumab includes the induction of cutaneous keratoacanthomas and/or squamous cell carcinomas in human cancer patients (see, for example: Lacouture *et al.,* 2015, Cancer Immunol Immunother, 64: 437-46; Stevenson *et al.,* 2013, OncoImmunology, 2:8, e26218; and Lonning *et al.*, 2011). Additional evidence from a clinical trial suggests that in some cases this antibody may accelerate tumor progression (Stevenson *et al.,* 2013, OncoImmunology, 2:8, e26218).

[007] Thus, new methods and compositions for modulating TGFβ signaling are necessary that can be used to effectively and safely treat diseases and disorders involving TGFβ, including, for example, cancer, fibrosis and inflammation.

[008] With an increasing recognition of potentially dangerous adverse effects associated with broad inhibition of TGFβ, a number of groups have more recently turned to identifying inhibitors that target a *subset* - but not all - of the isoforms and still retain sufficient efficacy. For example, WO 2016/161410 discloses neutralizing antibodies that bind both TGFβ1 and TGFβ2 (*i.e.,* TGFβ1/2 inhibitors). WO 2006/116002 provides neutralizing antibodies that bind both TGFβ1 and TGFβ3 (*i.e.,* TGFβ1/3 inhibitors), albeit preferentially to the former. In addition to traditional monoclonal antibodies, some groups are developing engineered fusion proteins that function as so-called "ligand traps" (see, for example, WO 2018/158727, WO 2018029367 and WO 2018129331), at least some of which may be selective for TGFβ1/3. Another class of TGFβ1/3 inhibitors include inhibitors of alpha-V (αv) integrins such as antibodies against αvβ6, which is an integrin known to activate both TGFβ1 and TGFβ3 (*i.e.,* TGFβ1/3). Yet others continue to pursue "better" pan-inhibitors that inhibit all three isoforms (*i.e.,* TGFβ1/2/3 or pan-inhibitors) (see, for example, WO 2018/134681).

[009] From an efficacy standpoint, however, the prevailing view of the field remains to be that it is advantageous to inhibit multiple isoforms of TGFβ to achieve therapeutic effects, and to accommodate this, toxicity management by "careful dosing regimen" is suggested as a solution (Brennan et al. (2018) mAbs, 10:1, 1-17).

[010] Recently, Applicant described isoform-selective TGFβ1 inhibitors which were demonstrated to be both safe and efficacious in animal models (see, for example: WO 2017/156500 and WO 2018/129329, incorporated by reference), supporting the notion that selectively targeting the TGFβ1 isoform, as opposed to broadly antagonizing all TGFβ isoforms, may provide an advantageous approach to achieving efficacy with acceptable toxicity.

[011] Whilst the observed safety profile achieved by selective inhibition of TGFβ1 at doses that were shown efficacious in vivo is a promising step towards developing a TGFβ1 inhibitor for clinical applications, identification of TGFβ1 inhibitors that are capable of selectively affecting a defined subset of TGFβ1 effects (*e.g.,* TGFβ inhibitors that are selective to LTBP-presented complexes) remained elusive. More recently, Applicant demonstrated that such "LTBP context-specific" inhibitors can be generated (WO 2019/023661, incorporated herein by reference) using the methods previously described by Applicant (see, for example, WO 2014/074532 and WO 2014/182676). However, the LTBP-selective TGFβ1 inhibitors described in the aforementioned international publication showed modest affinities and inhibitory activities, coupled with suboptimal cross-species reactivity.

SUMMARY

[012] The present disclosure provides improved TGFβ inhibitors capable of selectively targeting matrix-associated proTGFβ complexes, such as LTBP1-proTGFβ1 and LTBP3-proTGFβ1.

[013] These inhibitors bind and inhibit LTBP1- and/or LTBP3-presented proTGFβ at high affinities (at least nanomolar range) but do not bind and inhibit immune cell-associated TGFβ, *e.g.,* GARP- and/or LRRC33-presented proTGFβ1, or the binding is below meaningful levels (*e.g.,* at least 50 times affinities for the LTBP complexes over GARP or LRRC33 complex). Thus, these inhibitors can selectively inhibit activation of TGFβ in a context-dependent manner, such that they selectively bind, thereby inhibiting the TGFβ signaling axis associated with the ECM. In particular, the present disclosure includes selective inhibitors of matrix-associated (*e.g.,* LTBP1 and/or LTBP3-associated) TGFβ activation. In some examples, such inhibitors specifically bind a particular isoform of TGFβ (*e.g.,* proTGFβ1, proTGFβ2, and/or proTGFβ3) associated with LTBP1 and/or LTBP3, thus also providing TGFβ isoform specificity. In a particular example, such inhibitors specifically bind to LTBP1/3-proTGFβ1. In any of the examples of the present disclosure, such inhibitors do not inhibit activation of TGFβ1 associated with immune cell function, mediated by GARP and/or LRRC33. The improved antibodies encompassed by the present disclosure have affinities towards human LTBP1-proTGFβ1 and/or human LTBP3-proTGFβ1 in at least a nanomolar range (*i.e.,* 1 x 10^{-9}M to 10 x 10^{-9}M). In some examples, such antibodies also have affinities towards murine LTBP1-proTGFβ1 and/or murine LTBP3-proTGFβ1 in at least a nanomolar range (*i.e.,* 1 x 10^{-9}M to 10 x 10^{-9}M).

[014] Rationale for the therapeutic use of a TGFβ1 inhibitor that does not target the GARP-proTGFβ1 complex on regulatory T cells is at least threefold:

[015] First, regulatory T cells play a crucial role in maintaining immune tolerance to self-antigens and in preventing autoimmune disease. Since Tregs generally suppress, dampen or downregulate induction and proliferation of effector T cells, systemic inhibition of this function may lead to overactive or exaggerated immune responses in the host by disabling the "break" that is normally provided by Treg cells. Thus, the approach taken here (*e.g.,* TGFβ1 inhibition without disabling Treg function) is aimed to avoid the risk of eliciting autoimmunity. Furthermore, patients who already have a propensity for developing over-sensitive

immune responses or autoimmunity may be particularly at risk of triggering or exacerbating such conditions, without the availability of normal Treg function; and therefore, the inhibitors that selectively target the matrix TGFβ1 may advantageously minimize such risk.

[016] Second, evidence suggests that an alteration in the Th17/Treg ratio leads to an imbalance in pro-fibrotic Th17 cytokines, which correlate with severity of fibrosis, such as liver fibrosis (see, for example, Shoukry *et al.* (2017) J Immunol 198 (1 Supplement): 197.12). The present inventors reasoned that perturbation of the GARP arm of TGFβ1 function may directly or indirectly exacerbate fibrotic conditions.

[017] Third, regulatory T cells are indispensable for immune homeostasis and the prevention of autoimmunity. It was reasoned that, particularly for a TGFβ1 inhibition therapy intended for a long-term or chronic administration, it would be desirable to avoid potential side effects stemming from perturbation of normal Treg function in maintaining immune homeostasis (reviewed in, for example, Richert-Spuhler and Lund (2015) Prog Mol Biol Transl Sci. 136: 217–243). This strategy is at least in part aimed to preserve normal immune function, which is required, *inter alia*, for combatting infections.

[018] To this end, the inventors of the present disclosure set out to generate isoform-specific, context-selective inhibitors of TGFβ1 that selectively target matrix-associated TGFβ1 activation but not immune cell-associated TGFβ1 activation.

[019] Technical challenges that exist to date include limited ability to discern and selectively modulate these subpools of TGFβ1 present in various contexts (or "niches") in vivo.

[020] In an effort to address this challenge, the present inventors have identified isoform-specific monoclonal antibodies that bind the latent TGFβ1 prodomain, with no detectable binding to latent TGFβ2 or TGFβ3, and that inhibit integrin-mediated activation of latent TGFβ1 *in vitro* with the context-dependency as described herein. The discovery and characterization of such antibodies was made possible, at least in part, by the development of context-dependent cell-based assays of TGFβ1 activation. In the process of this novel assay development and validation, it was demonstrated that, like the αVβ6 integrin, αVβ8 can also activate LTBP1-proTGFβ1. It was further demonstrated that, similar to the LTBP1 complex, LTBP3-proTGFβ1 can be activated by αVβ6. Antibodies discovered by screening in these assays revealed a class of antibodies that binds and inhibits TGFβ1 only when presented by LTBP1 or LTBP3. Such LTBP-specific antibodies do not inhibit TGFβ1 in the context of the immune-associated TGFβ1 presenters GARP and LRRC33. Such antibodies are therapeutic candidates for the treatment of disorders including, *e.g.,* fibrotic conditions, and could allow chronic dosing that would avoid TGFβ-related immune system activation. Methods of selecting a context-specific or context-independent TGFβ1 inhibitor for various fibrotic conditions are also provided herein.

[021] Accordingly, in one example, the disclosure provides isoform-specific TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D \leq 50$ nM. In one example, the disclosure provides isoform-specific TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind

selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D \leq 25$ nM. In one example, the disclosure provides isoform-specific TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D \leq 10$ nM. In one example, the disclosure provides an isolated antibody, or antigen-binding portion thereof, that selectively binds to a LTBP1-proTGFβ1 complex and a LTBP3-proTGFβ1 complex, wherein the antibody, or antigen-binding portion thereof, does not bind to one or more of the following targets: (a) LTBP1 alone; (b) proTGFβ1 alone; (c) a GARP-proTGFβ1 complex; and (d) a LRRC33-proTGFβ1 complex. In further examples, the disclosure provides isoform-specific TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ1 complex and/or a LTBP3-TGFβ1 complex with a $K_D < 5$ nM.

[022] In one example, the disclosure provides inhibitors of extracellular matrix-associated TGFβ activation, which selectively bind a LTBP1/3-presented proTGFβ latent complex. In one example, the inhibitor does not inhibit immune cell-associated TGFβ1 activation, for example, immune cell-associated TGFβ1 activation that results from activation of a GARP-presented proTGFβ1 latent complex. In exemplary examples, the inhibitor is an antibody, or antigen-binding portion thereof.

[022a] In one aspect, the present disclosure refers to an antibody, or antigen-binding fragment thereof, which specifically binds human LTBP1-TGFβ1 complex and human LTBP3-TGFβ1 complex, comprising the following six CDRs: a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein: X_1 is S or R; and X_2 is G or S; b) CDR-H2 comprising the amino acid sequence (X_1)ISHEGS(X_2)KYYADSVKG, wherein: X_1 is V or S; X_2 is F or L; and c) CDR-H3 comprising the amino acid sequence ARPRI(X_1)ARRGGFGY, wherein X_1 is A or L; d) CDR-L1 as set forth in SEQ ID NO:97, comprising up to three amino acid changes; e) CDR-L2 as set forth in SEQ ID NO:98, comprising up to three amino acid changes; and f) CDR-L3 as set forth in SEQ ID NO:99, comprising up to three amino acid changes.

[023] In other examples, the disclosure provides TGFβ antibodies, or antigen-binding fragments thereof, characterized in that they bind selectively to an LTBP1-TGFβ complex and/or a LTBP3-TGFβ complex. In some examples, the antibodies, or antigen-binding fragments thereof, selectively bind to LTBP1-TGFβ1. In some examples, such antibodies bind both human and murine counterparts.

[024] In one example, the disclosure provides an isolated antibody, or antigen-binding portion thereof, that selectively binds an LTBP1-proTGFβ latent complex and/or an LTBP3-proTGFβ latent complex, thereby modulating release of mature TGFβ growth factor from the latent complex, wherein the antibody, or antigen-binding portion thereof, does not bind mature TGFβ1 alone or a GARP-proTGFβ1 latent complex. In one example, the antibody, or antigen-binding portion thereof, does not bind an LRRC33-proTGFβ1 latent complex. Alternatively, in one example, the antibody, or antigen-binding portion thereof, binds an LRRC33-proTGFβ1 latent complex.

[025] In some examples, the antibody, or antigen-binding portion thereof, is specific to an LTBP1-proTGFβ1 latent complex. In other examples, the antibody, or antigen-binding portion thereof, is specific to an LTBP3-proTGFβ1 latent complex. In one example, the antibody, or antigen-binding portion thereof, binds an LTBP1-proTGFβ1 complex and/or a LTBP3-proTGFβ1 complex with a dissociation constant (K_D) of at least about 10^{-8} M. In one example, the antibody, or antigen-binding portion thereof, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In one example, the antibody, or antigen-binding portion thereof, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In one example, the antibody, or antigen-binding portion thereof, binds a mouse LTBP1-proTGFβ1 complex and/or a mouse LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In one example, the antibody, or antigen-binding portion thereof, binds a mouse LTBP1-proTGFβ1 complex and/or a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[026] The present disclosure further provides antibodies and antigen binding fragments thereof, which selectively bind an LTBP1-proTGFβ complex and/or an LTBP3-proTGFβ complex and have one or more yet further advantageous properties. Indeed, the inventors surprisingly found that such antibodies could be provided which bind a human LTBP1-proTGFβ complex and a human LTBP3-proTGFβ complex with high affinity, and advantageously slow dissociation rates, while also being cross-reactive with mouse LTBP1-proTGFβ complex and mouse LTBP3-proTGFβ complex and displaying no significant binding to human GARP-proTGFβ complex (or indeed to human LRRC33-proTGFβ complex).

[027] Further still, antibodies disclosed herein (including antibodies having one or more, or even all of the aforementioned advantageous properties) exhibit potent inhibition of TGFβ1 signaling in cell-based assays, and significantly reduce markers of fibrosis and TGFβ signaling in multiple animal models of fibrosis.

[028] Thus, in some examples, the antibody, or antigen-binding fragment thereof binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by BLI, and has one or more of the following properties:

i) is cross-reactive with mouse LTBP1-proTGFβ1 complex;

ii) is cross-reactive with mouse LTBP3-proTGFβ1 complex;

iii) binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured by BLI;

iv) binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured by BLI;

v) binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower than the K_D when binding to a human GARP-proTGFβ1 complex under the same assay conditions;

vi) does not show detectable binding to a human GARP-proTGFβ1 complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex;

vii) does not show detectable binding to an LRRC33-proTGFβ1 complex (*e.g.,* a human LRRC33-proTGFβ1 complex) as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and/or human LTBP3-TGFβ1 complex.

[029] In some examples, the antibody or antigen-binding fragment has at least properties (i)-(v) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (i)-(iv) and (vi) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (i), (iii) and (v) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (ii), (iv) and (v) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (i), (iii) and (vi) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (ii), (iv) and (vi) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (i)-(iii) and (v) above, and optionally (vii). In some examples, the antibody or antigen-binding fragment has at least properties (i)-(iii) and (vi) above, and optionally (vii).

[030] In some preferred examples, the antibody or antigen-binding fragment binds a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by BLI, and has all of the above properties (i)-(vii).

[031] The antibody or antigen-binding fragment may selectively bind a LTBP1/3-presented proTGFβ latent complex and inhibit extracellular matrix-associated TGFβ activation.

[032] Further still, further advantageous isoform-selective inhibitors of TGFβ1 activation may include monoclonal antibodies (including immunoglobulins and antigen-binding fragments or portions thereof) that exhibit slow dissociation rates (*i.e.,* off-rates, k_{OFF}). Thus, the disclosure is further based on the recognition that treatment of chronic and progressive disease such as fibrosis may require inhibitors with superior durability, which may be reflected on the dissociation rate of such antibody.

[033] The affinity of an antibody to its antigen is typically measured as the equilibrium dissociation constant, or K_D. The ratio of the experimentally measured off- and on-rates (k_{OFF} / k_{ON}) can be used to calculate the K_D value. The k_{OFF} value represents the antibody dissociation rate, which indicates how quickly it dissociates from its antigen, whilst the k_{ON} value represents the antibody association rate which provides how quickly it binds to its antigen. The latter is typically concentration-dependent, while the former is concentration-independent. The K_D value relates to the concentration of antibody (the amount of antibody needed for a particular experiment) and so the lower the K_D value (lower concentration) and thus the higher the affinity of the antibody. With respect to a reference antibody, a higher affinity antibody may have a lower k_{OFF} rate, a higher k_{ON} rate, or both.

[034] Both the k_{OFF} and k_{ON} rates contribute to the overall affinity of a particular antibody to its antigen, and relative importance or impact of each component may depend on the mechanism of action of the

antibody. For example, neutralizing antibodies, which bind mature growth factors (*e.g.,* soluble, transient TGFβ1 ligand liberated from a latent complex), must compete with the endogenous high-affinity receptors for ligand binding in vivo. Because the ligand-receptor interaction is a local event and because the ligand is short-lived, such antibodies must be capable of rapidly targeting and sequestering the soluble growth factor before the ligand finds its cellular receptor – thereby activating the TGFβ1 signaling pathway – in the tissue. Therefore, for ligand-targeting neutralizing antibodies to be potent, the ability to bind the target growth factor fast, *i.e.,* high association rates (k_{ON}), may be especially important.

[035] By contrast, Applicant reasoned that antibodies that inhibit the TGFβ1 signaling by preventing the activation (*e.g.,* release) of mature growth factor from the latent complex ("activation inhibitors") may preferentially benefit from having slow dissociation rates once the antibody is engaged with the target antigen (*e.g.,* proTGFβ1 complexes). Unlike neutralizing antibodies, such antibodies do not directly compete with cellular receptors; rather, they work upstream of the signaling by targeting inactive precursor forms (*e.g.,* latent proTGFβ1 complexes) that remain dormant within a tissue environment thereby preemptively preventing the activation of TGFβ1. Such antibodies may exert their inhibitory activity by preventing mature growth factor from being liberated from the latent complex. For example, such antibodies may function like a "clamp" to lock the active growth factor in the prodomain cage structure to keep it in an inactive (*e.g.,* "latent") state. Indeed, structural analyses, including epitope mapping, provided insight into the molecular mechanism underlining the ability of these antibodies to block TGFβ1 activation. In this regard, the Latency Lasso region of the prodomain may be a particularly useful target.

[036] Upon target engagement, antibodies that are able to remain bound to the target (*e.g.,* dissociate very slowly from the latent complex) are expected to be advantageous in achieving superior in vivo potency, due to enhanced durability of effects and/or avidity. Based on this recognition, Applicant of the present disclosure sought to identify isoform-selective activation inhibitors of TGFβ1 with particularly low k_{OFF} values as compared to previously described antibodies. Thus, according to the disclosure, preferred antibodies have high affinities primarily attributable to a slow dissociation rate (k_{OFF}), as opposed to fast association rate (k_{ON}). Accordingly, in some examples, the antibody, or antigen-binding fragment thereof binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by BLI, and has one or more of the following properties (which may be in addition to one of properties (i)-(vii), or combinations thereof set out above):

(viii) low dissociation rates (k_{OFF}) of $\leq 5 \times 10^{-4}$ (1/s), when binding human LTBP1-proTGFβ1 complex and/or human LTBP3-TGFβ1 complex (*e.g.,* as measured by a suitable in vitro binding/kinetics assay, such as by BLI, *e.g.,* Octet-based systems); and/or

(ix) long half-binding time (t½) of ≥ 45 minutes when bound to human LTBP1-proTGFβ1 and/or human LTBP3-proTGFβ1 complex (*e.g.,* as measured by SPR).

[037] In some preferred examples, the antibody or antigen binding fragment comprises the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTFRSYVMH (SEQ ID NO: 166);

b) CDR-H2 comprising the amino acid sequence VISHEGS(X_1)KYYADSVKG, wherein: X_1 is L or G (SEQ ID NO: 366); and

c) CDR-H3 comprising the amino acid sequence A(X_1)PRIAARRGGFG(X_2), wherein: X_1 is V, R or L; and X_2 is Y, S or T (SEQ ID NO: 367);

d) CDR-L1 comprising the amino acid sequence TRS(X_1)G(X_2)ID(X_3)NYVQ, wherein, X_1 is S or H; X_2 is N, L, S or A; and X_3 is N, D or Y (SEQ ID NO: 368);

e) CDR-L2 comprising the amino acid sequence ED(X_1)(X_2)RPS, wherein: X_1 is N, F or A; and X_2 is Q, I or V (SEQ ID NO: 369); and

f) CDR-L3 comprising the amino acid sequence Q(X_1)YD(X_2)(X_3)(X_4)Q(X_5)VV, wherein: X_1 is S or G; X_2 is S, F, Y, D, H or W; X_3 is N, D or S; X_4 is N, A, L, E or T; and X_5 is G, R, A or L (SEQ ID NO: 370).

[038] In some preferred examples, the antibody or antigen-binding fragment thereof competes or cross-competes with an antibody having a heavy chain variable region sequence as set forth in SEQ ID NO: 318 and light chain variable region sequence as set forth in SEQ ID NO: 319 (*e.g.,* Ab42). The antibody may comprise a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 318 and a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 319.

[039] The antibody or antigen-binding fragment thereof provided herein may, in some preferred examples, comprise the following six CDRs (*e.g.,* those of Ab42):

CDR-H1 comprising the amino acid sequence FTFRSYVMH (SEQ ID NO: 166);

CDR-H2 comprising the amino acid sequence VISHEGSLKYYADSVKG (SEQ ID NO: 167);

CDR-H3 comprising the amino acid sequence ARPRIAARRGGFGY (SEQ ID NO: 168);

CDR-L1 comprising the amino acid sequence TRSSGNIDNNYVQ (SEQ ID NO: 169);

CDR-L2 comprising the amino acid sequence EDNQRPS (SEQ ID NO: 170); and

CDR-L3 comprising the amino acid sequence QSYDYDTQGVV (SEQ ID NO: 171).

[040] The antibody or antigen-binding fragment may further comprise a heavy chain variable region having an amino acid sequence that is at least 95% identical (optionally at least 98% identical) to SEQ ID NO: 318 and a light chain variable region having an amino acid sequence that is at least 95% identical (optionally at least 98% identical) to SEQ ID NO: 319.

[041] In some alternative examples, the antibody, or antigen-binding fragment thereof, comprises the following six CDRs:

a) CDR-H1 comprising the amino acid sequence GSIRSSSYYWG (SEQ ID NO: 292);

b) CDR-H2 comprising the amino acid sequence SISYSATTYY (SEQ ID NO: 293);

c) CDR-H3 comprising the amino acid sequence A(X_1)DPSYDS(X_2)AGM(X_3)V, wherein: X_1 is S or G; X_2 is A or I; and X_3 is D or Q (SEQ ID NO: 371);

d) CDR-L1 comprising the amino acid sequence RAS(X_1)(X_2)IS(X_3)YLN, wherein: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y (SEQ ID NO: 389);

e) CDR-L2 comprising the amino acid sequence (X_1)AS(X_2)(X_3)QS, wherein: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R (SEQ ID NO: 390);

f) CDR-L3 comprising the amino acid sequence QQ(X_1)(X_2)D(X_3)P(X_4)T, wherein: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L (SEQ ID NO: 391).

[042] In some examples, the antibody or antigen-binding fragment thereof competes or cross-competes with an antibody having a heavy chain variable region sequence as set forth in SEQ ID NO: 360 and light chain variable region sequence as set forth in SEQ ID NO: 361 (*e.g.,* Ab63). The antibody may comprise a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 360 and a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 361.

[043] The antibody or antigen-binding fragment thereof provided herein may comprise the following six CDRs (*e.g.,* those of Ab63):

CDR-H1 comprising the amino acid sequence GSIRSSSYYWG (SEQ ID NO: 292);

CDR-H2 comprising the amino acid sequence SISYSATTYY (SEQ ID NO: 293);

CDR-H3 comprising the amino acid sequence AGDPSYDSIAGMQV (SEQ ID NO: 294);

CDR-L1 comprising the amino acid sequence RASQSISSYLN (SEQ ID NO: 295);

CDR-L2 comprising the amino acid sequence AASNLQS (SEQ ID NO: 296); and

CDR-L3 comprising the amino acid sequence QQSFDWPLT (SEQ ID NO: 297).

[044] The antibody or antigen-binding fragment may further comprise a heavy chain variable region having an amino acid sequence that is at least 95% identical (optionally at least 98% identical) to SEQ ID NO: 360 and a light chain variable region having an amino acid sequence that is at least 95% identical (optionally at least 98% identical) to SEQ ID NO: 361.

[044a] In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody as disclosed herein and a pharmaceutically acceptable excipient.

[044b] In another aspect, the present disclosure refers to a composition comprising a multi-dose vial containing the pharmaceutical composition as disclosed herein.

[044c] In another aspect, the present disclosure refers to a composition comprising a single-dose syringe containing the pharmaceutical composition as disclosed herein, optionally wherein the syringe is a disposable syringe.

[044d] In another aspect, the present disclosure refers to the use of the composition as disclosed herein in the manufacture of a medicament for treating a fibrotic disorder in a human subject.

[044e] In another aspect, the present disclosure refers to the composition as disclosed herein for use in therapy.

[045] In one example, the disclosure provides an antibody, or antigen-binding fragment thereof, for use in a method for treating a fibrotic disorder in a subject, wherein the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ1 complex;, wherein: a) the fibrotic disorder comprises chronic

inflammation; b) the subject benefits from immune suppression; c) the subject has or is at risk of developing an autoimmune disease; d) the subject is a candidate for or has received an allograft transplant; e) the subject has an elevated Th17/Treg ratio; and/or, f) the subject is in need of a long-term or chronic administration of the TGFβ1 inhibitor. In some examples, the the subject has or is at risk of developing a metabolic disorder (and the subject is optionally a subject according to one or more of a)-f)). In some examples, the the antibody, or antigen-binding fragment thereof, is an isoform-specific LTBP1-proTGFβ1 inhibitor and/or LTBP3-proTGFβ1 inhibitor.

[046] The antibodies or antigen-binding fragments therof provided herein may be used in a method for treating a fibrotic disorder in a subject. The fibrotic disorder may comprise chronic inflammation. The subject may benefit from immune suppression. The subject may have or be at risk of developing an autoimmune disease. The subject may be a candidate for or may have received an allograft transplant.

[047] Alternatively, or in addition, the subject may have an elevated Th17/Treg ratio. The subject may be in need of a long-term or chronic administration of the TGFβ1 inhibitor.

[048] Alternatively, or in addition, the subject may have or be at risk of developing a metabolic disorder.

[048a] In another aspect, the present disclosure refers to a method for making a composition as disclosed herein, comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, , wherein the antibody, or the antigen-biding fragment thereof, does not show detectable binding to a human GARP-proTGFβ1 or human LRRC33-proTGFβ1 complex, the method comprising steps of: i) selecting an antibody or an antigen-binding fragment thereof that dissociates from human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex with t½ of at least 45 minutes, and, ii) formulating the antibody or fragment into a pharmaceutical composition, thereby making the composition comprising the antibody or antigen-binding fragment.

[049] In another example, the disclosure provides a method for making a composition comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody, or antigen-binding fragment thereof, inhibits TGFβ1 but does not inhibit TGFβ2 or TGFβ3, the method comprising steps of i) providing at least one antigen comprising LTBP1-proTGFβ1 and/or LTBP3-proTGFβ1, ii) selecting a first pool of antibodies, or antigen-binding fragments thereof, that specifically bind the at least one antigen of step (i) so as to provide specific binders of LTBP1-proTGFβ1 and/or LTBP3-proTGFβ1; iii) selecting a second pool of antibodies, or antigen-binding fragments thereof, that inhibit activation of TGFβ1, so as to generate specific inhibitors of TGFβ1 activation; iv) formulating an antibody, or antigen-binding fragment thereof, that is present in the first pool of antibodies and the second pool of antibodies into a pharmaceutical composition, thereby making the composition comprising the antibody, or antigen-binding fragment thereof.

[050] In one example, the method further comprises a step of removing from the first pool of antibodies, or antigen-binding fragments thereof, any antibodies, or antigen-binding fragments thereof, that bind GARP-proTGFβ1, LRRC33-proTGFβ1, mature TGFβ1, GARP-proTGFβ2, LRRC33-proTGFβ2, mature TGFβ2, GARP-proTGFβ3, LRRC33-proTGFβ3, mature TGFβ3, or any combinations thereof. In one example, the method further comprises a step of determining or confirming isoform-specificity of the antibodies, or antigen-binding fragments thereof, selected in steps (ii) and/or (iii). In one example, the method further comprises a step of selecting for antibodies, or antigen-binding fragments thereof, that are cross-reactive to human and rodent antigens. In one example, the method further comprises a step of generating a fully human or humanized antibody, or antigen-binding fragment thereof, of the antibody, or antigen-binding fragment thereof, that is present in the first pool of antibodies and the second pool of antibodies.

[051] In one example, the method further comprises a step of subjecting the antibody, or antigen-binding fragment thereof, that is present in the first pool of antibodies and the second pool of antibodies to affinity maturation and/or optimization, so as to provide an affinity matured and/or optimized antibody or fragment thereof. In one example, the affinity maturation/optimization comprises a step of subjecting the antibody, or antigen-binding fragment thereof, that is present in the first pool of antibodies and/or the second pool of antibodies to light chain shuffling as described herein. In one example, the affinity maturation/optimization comprises the step of subjecting the antibody, or antigen-binding fragment thereof, that is present in the first, second, and/or third pool of antibodies to CDR H1/H2 diversification as described herein. In one example, the affinity maturation/optimization comprises the step of subjecting the antibody, or antigen-binding fragment thereof, to CDR-H3 mutagenesis as described herein. In one example, the affinity maturation/optimization comprises the step of subjecting the antibodies, or antigen-binding fragment thereof, to light chain CDR mutagenesis as described herein. In one example, the affinity maturation/optimization comprises the step of subjecting the antibodies, or antigen-binding fragment thereof, to light chain CDR L1/L2 diversification as described herein.

[052] In one example, the method further comprises a step of determining affinity of the antibodies, or antigen-binding fragments thereof, from the first and/or second pools of antibodies to human LTBP1-proTGFβ1 and/or human LTBP3-proTGFβ1. In some examples, the method further comprises a step of removing from the first and/or second pools of antibodies, or antigen-binding fragments thereof, any antibodies, or antigen-binding fragments thereof, that bind to human LTBP1-proTGFβ1 and/or human LTBP3-proTGFβ1 with a K_D of > 100 nM, > 50 nM, > 25 nM, or > 10 nM, as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[053] In one example, the method further comprises a step of determining affinity of the antibodies, or antigen-binding fragments thereof, from the first and/or second pools to mouse LTBP1-proTGFβ1 and/or mouse LTBP3-proTGFβ1. In some examples, the method further comprises a step of removing from the first and/or second pools of antibodies, or antigen-binding fragments thereof, any antibodies, or antigen-binding fragments thereof, that bind to mouse LTBP1-proTGFβ1 and/or mouse LTBP3-proTGFβ1 with a

K_D of > 100 nM, > 50 nM, or > 10 nM, as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[054] In one example, the method further comprises a step of removing from the first and/or second pools of antibodies, or antigen-binding fragments thereof, any antibodies, or antigen-binding fragments thereof, that do not bind mouse LTBP1-proTGFβ1 and/or mouse LTBP3-proTGFβ1.

[055] In one example, the method further comprises a step of determining the IC_{50} of the antibodies, or antigen-binding fragments thereof, from of the first and/or second pools of antibodies, or antigen-binding fragments thereof, as measured by a suitable functional in vitro cell-based assay such as a caga assay, as described herein. In some examples, the method comprises the step of removing antibodies, or antigen-binding fragments thereof, from the first and/or second pools of antibodies, or antigen-binding fragments thereof, that have an IC_{50} of greater than 100 nM, 50 nM, 25 nM, 10 nM, or 5 nM as measured by a cell-based assay (such as a caga assay) as described herein.

[056] In some examples, the method comprises the step of removing antibodies, or antigen-binding fragments thereof, from the first and/or second pools, antibodies, or antigen-binding fragments thereof, that have an IC_{50} of greater than 50 nM or 10 nM as measured by an endogenous LTBP caga assay as described herein.

[057] In some examples, the method comprises the step of removing antibodies, or antigen-binding fragments thereof, from the first and/or second pools, antibodies, or antigen-binding fragments thereof, that have an IC_{50} of greater than 50 nM, 25 nM, or 10 nM, as measured by a human LTBP overexpression caga assay as described herein.

[058] In some examples, the method comprises the step of removing antibodies, or antigen-binding fragments thereof, from the first and/or second pools, antibodies, or antigen-binding fragments thereof, that have an IC_{50} of greater than 50 nM, 25 nM, 10 nM, or 5 nM, as measured by a murine LTBP overexpression caga assay as described herein.

[059] Processes and methods for identifying or selecting TGFβ1-selective inhibitors suitable for therapeutic use are encompassed by the disclosure, as are methods for making a composition comprising a TGFβ1-selective inhibitor. In preferred examples, a TGFβ1 inhibitor (*e.g.,* a selected inhibitor) includes one or more antibodies or antigen-binding fragments with particularly advantageous kinetics criteria characterized by: i) high affinities to each of human LTBP1/3-proTGFβ1 complexes (*e.g.,* K_D < 5 nM), and, ii) low dissociation rates (k_{OFF}), *e.g.,* ≤ 5 x 10^{-4} (1/s), as measured by a suitable in vitro binding/kinetics assay, such as by BLI, *e.g.,* Octet-based systems. The low dissociation rate criterion may be reflected in long dissociation half-time (t½), *e.g.,* ≥ 45 minutes from human LTBP1-proTGFβ1 and/or human LTBP3-proTGFβ1 complexes. Preferably, the long dissociation half-time of an antibody or antigen-binding fragment thereof for the matrix-associated complex(es) is coupled with short dissociation half-time with respect to cell-assosciated complexes, *e.g.,* human GARP-proTGFβ1 and/or human LRRC33-proTGFβ1 complexes. In particular, preferred antibodies or fragments dissociate from human

GARP-proTGFβ1 complex with t ½ of no more than 10 minutes, more preferably no more than 5 minutes. Likewise, methods for making a composition comprising a TGFβ1-selective inhibitor as described herein may further include a step of selecting such antibodies. The selected antibody or the plurality of antibodies are evaluated in preclinical studies comprising an efficacy study and a toxicology/safety study, employing suitable preclinical models. Effective amounts of the antibody or the antibodies determined in the efficacy study are below the level that results in undesirable toxicities determined in the toxicology/safety study. Preferably, the antibody or antibodies are selected which has/have at least 3-fold, 6-fold, and more preferably 10-fold therapeutic window. Effective amounts of the antibodies according to the present disclosure may be between about 0.1 mg/kg and about 30 mg/kg when administered weekly. In preferred examples, the maximally tolerated dose (MTD) of the antibodies according to the present disclosure is >100 mg/kg when dosed weekly for at least 4 weeks. In some examples, in a preclinical toxicology study, the antibodies show a NOAEL of >100 mg/kg/week, >200 mg/kg/week or >300 mg/kg/week, wherein optionally the toxicology study is a 4-week study, 8-week study, or a 12-week study. For example, the NOAEL is >100 mg/kg/week in a 12-week sub-chronic dosing regimen in healthy mice or rats.

[060] The present disclosure also includes a surprising finding that inhibition of TGFβ3 with a TGFβ3-selective inhibitor produced *pro-fibrotic* effects in mice. Similarly, concurrent inhibition of both TGFβ1 and TGFβ3 in the same model with a combination of a TGFβ1-selective inhibitor and a TGFβ3-selective inhibitor resulted in attenuated anti-fibrotic effects of the TGFβ1 inhibitor. These observations raise the possibility that non-selective TGFβ inhibitors (such as pan-inhibitors and TGFβ1/3 inhibitors) may in fact exacerbate fibrosis. Advantageously, the antibodies disclosed herein (*e.g.,* Ab42 and variants thereof, as described herein) are isoform-selective in that they specifically target the latent TGFβ1 complex and do so with low dissociation rates. Thus, the disclosure includes the recognition that when selecting a particular TGFβ inhibitor for patients with a fibrotic condition (*e.g.,* disease involving ECM dysregulation), isoform selectivity should be carefully considered so as to avoid risk of exacerbating ECM dysregulation. Accordingly, the present disclosure includes therapeutic methods comprising selecting a TGFβ inhibitor that does not inhibit TGFβ3 to treat a subject with a fibrotic condition, (including preferred fibrotic conditions, as described herein).

[061] The isoform-selective LTBP1/3- proTGFβ1 complex-selective inhibitor as used herein may in some examples be selected from Ab31, Ab34, Ab37, Ab38, Ab39, Ab40, Ab41, Ab42, Ab43, Ab44, Ab45, Ab62, Ab63, and Ab64 (optionally Ab42 or Ab63) (*i.e.,* an antibody or antigen-binding fragment having the heavy and light chain variable regions of the corresponding Ab, as provided herein), a variant/derivative or antigen-binding fragment thereof thereof, or an engineered molecule comprising an antigen-binding fragment thereof. In some preferred examples, the LTBP1/3- proTGFβ1 complex-selective inhibitor inhibitor is Ab42, a variant/derivative or antigen-binding fragment thereof, or an engineered molecule comprising an antigen-binding fragment thereof. In preferred examples, the LTBP1/3- proTGFβ1 complex-selective inhibitor is Ab42 or an antigen-binding fragment thereof.

BRIEF DESCRIPTION OF THE FIGURES

[062] **Fig. 1** graphically depicts that targeting of the latent form of TGFβ1 provides isoform and context specificity.

[063] **Figs. 2A-2B** demonstrate the identification of isoform-specific and LTBP complex-specific binders of latent TGFβ1. **Fig. 2A** demonstrates that SR-AB1 binds latent TGFβ1, independent of the presenting molecule. SR-AB1 is a human monoclonal antibody that was discovered by yeast display, which selectively binds latent TGFβ1, without detectable binding to latent TGFβ2, TGFβ3, or mature TGFβ1. SR-AB1 cross-reacts with mouse, rat, and cynomolgus monkey proteins and binds to all four latent TGFβ1 complexes. **Fig. 2B** demonstrates that SR-AB2, an anti-LTBP1-proTGFβ1 antibody, does not bind GARP-proTGFβ1 or mature TGFβ1. SR-AB2 cross-reacts with rodent LTBP1-proTGFβ1.

[064] **Figs. 3A-3B** demonstrate functional assays (potency assays) to detect the inhibition of activated recombinant latent TGFβ1. **Fig. 3A** depicts the activation of latent TGFβ1 deposited in the extracellular matrix (ECM). In this assay, presenting molecules are co-transfected with proTGFβ1 in integrin-expressing cells. Transiently transfected cells are seeded in assay plates in the presence of inhibitors. Latent LTBP-proTGFβ1 complex is embedded in the ECM. TGFβ reporter cells are then added to the system; free growth factor (released by integrin) signals and is detected by luciferase assay. **Fig. 3B** depicts the activation of latent TGFβ1 presented on the cell surface. Presenting molecules are co-transfected with proTGFβ1 in integrin-expressing cells. Latent TGFβ1 is expressed on the cell surface by GARP or LRRC33. TGFβ reporter cells and inhibitors are then added to the system; free growth factor (released by integrin) signals and is detected by luciferase assay.

[065] **Figs. 4A-4B** depict the optimization of the recombinant functional assays. **Fig. 4A** depicts the relative contribution of presenting molecule and/or proTGFβ1 activation upon co-transfection of presenting molecule and proTGFβ1. **Fig. 4B** depicts the optimization of co-transfection: the ratio of

CDRL2	EDNVRPS (SEQ ID NO: 224)
CDRL3	QSYDYDNQAVV (SEQ ID NO: 225)
Antibody	**SR-AB52**
CDRH1	FTFRSYVMH (SEQ ID NO: 226)
CDRH2	VISHEGSGKYYADSVKG (SEQ ID NO: 227)
CDRH3	ARPRIAARRGGFGT (SEQ ID NO: 228)
CDRL1	TRSSGNIDYNYVQ (SEQ ID NO: 229)
CDRL2	EDNVRPS (SEQ ID NO: 230)
CDRL3	QSYDYDTQGVV (SEQ ID NO: 231)
Antibody	**SR-AB53**
CDRH1	FTFRSYVMH (SEQ ID NO: 232)
CDRH2	VISHEGSGKYYADSVKG (SEQ ID NO: 233)
CDRH3	ARPRIAARRGGFGT (SEQ ID NO: 234)
CDRL1	TRSSGNIDYNYVQ (SEQ ID NO: 235)
CDRL2	EDNVRPS (SEQ ID NO: 236)
CDRL3	QGYDWDTQGVV (SEQ ID NO: 237)
Antibody	**SR-AB54**
CDRH1	FTFRSYVMH (SEQ ID NO: 238)
CDRH2	VISHEGSGKYYADSVKG (SEQ ID NO: 239)
CDRH3	ALPRIAARRGGFGS (SEQ ID NO: 240)
CDRL1	TRSSGNIDYNYVQ (SEQ ID NO: 241)
CDRL2	EDNVRPS (SEQ ID NO: 242)

CDRL3	QSYDSDNQRVV (SEQ ID NO: 243)
Antibody	**SR-AB55**
CDRH1	FTFRSYVMH (SEQ ID NO: 244)
CDRH2	VISHEGSGKYYADSVKG (SEQ ID NO: 245)
CDRH3	ALPRIAARRGGFGS (SEQ ID NO: 246)
CDRL1	TRSSGNIDYNYVQ (SEQ ID NO: 247)
CDRL2	EDNVRPS (SEQ ID NO: 248)
CDRL3	QSYDYDNQAVV (SEQ ID NO: 249)
Antibody	**SR-AB56**
CDRH1	FTFRSYVMH (SEQ ID NO: 250)
CDRH2	VISHEGSGKYYADSVKG (SEQ ID NO: 251)
CDRH3	ALPRIAARRGGFGS (SEQ ID NO: 252)
CDRL1	TRSSGNIDYNYVQ (SEQ ID NO: 253)
CDRL2	EDNVRPS (SEQ ID NO: 254)
CDRL3	QSYDYDTQGVV (SEQ ID NO: 255)
Antibody	**SR-AB57**
CDRH1	FTFRSYVMH (SEQ ID NO: 256)
CDRH2	VISHEGSGKYYADSVKG (SEQ ID NO: 257)
CDRH3	ALPRIAARRGGFGS (SEQ ID NO: 258)
CDRL1	TRSSGNIDYNYVQ (SEQ ID NO: 259)
CDRL2	EDNVRPS (SEQ ID NO: 260)
CDRL3	QGYDWDTQGVV (SEQ ID NO: 261)
Antibody	**SR-AB58**

proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[312] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3 and does not bind to human GARP-proTGFβ1.

[313] In another aspect, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the asparagine residue at position 4 of SEQ ID NO:94 may be substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine. SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399.

[314] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:94, with the proviso that (i) the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine; (ii) the asparagine residue at position 4 of SEQ ID NO:94 may be

substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine; (iii) the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine; (iv) the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine; (v) the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine; (vi) the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine; and/or, (vii) the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine. SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399.

[315] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises three heavy chain CDRs and three light chain CDRs, wherein the heavy chain CDRs comprise:

a) CDR-H1: SEQ ID NO:94 (SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399), with the proviso that:
   i. the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine;
   ii. the asparagine residue at position 4 of SEQ ID NO:94 may be substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine;
   iii. the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine;
   iv. the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine;
   v. the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine;
   vi. the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine; and/or,
   vii. the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine;
b) CDR-H2: SEQ ID NO:95, optionally comprising one or more amino acid changes; and
c) CDR-H3: SEQ ID NO:96, optionally comprising one or more amino acid changes.

[316] In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[317] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:94 (SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399), with the proviso that:
   i. the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine;
   ii. the asparagine residue at position 4 of SEQ ID NO:94 may be substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine;
   iii. the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine;
   iv. the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine;
   v. the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine;
   vi. the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine; and/or,
   vii. the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine;
b) CDR-H2: SEQ ID NO:95, optionally comprising one or more amino acid changes;
c) CDR-H3: SEQ ID NO:96, optionally comprising one or more amino acid changes;
d) CDR-L1: SEQ ID NO:97, optionally comprising one or more amino acid changes;
e) CDR-L2: SEQ ID NO:98, optionally comprising one or more amino acid changes; and,
f) CDR-L3: SEQ ID NO:99, optionally comprising one or more amino acid changes.

[318] In some embodiments, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

[319] In a particular embodiment, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3; wherein the antibody is a fully human or humanized antibody or a fragment thereof, and wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:94 (SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399), with the proviso that:

i. the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine;
ii. the asparagine residue at position 4 of SEQ ID NO:94 may be substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine;
iii. the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine;
iv. the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine;
v. the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine;
vi. the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine; and/or,
vii. the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine;

b) CDR-H2: SEQ ID NO:95, optionally comprising one or more amino acid changes;
c) CDR-H3: SEQ ID NO:96, optionally comprising one or more amino acid changes;
d) CDR-L1: SEQ ID NO:97, optionally comprising one or more amino acid changes;
e) CDR-L2: SEQ ID NO:98, optionally comprising one or more amino acid changes; and,
f) CDR-L3: SEQ ID NO:99, optionally comprising one or more amino acid changes.

[320] In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[321] In another embodiment, such antibody is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, such antibody is also cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[322] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is also isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

[323] In another aspect, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392). In some embodiments, X_1 is S. In some embodiments, X_1 is R. In some embodiments, X_2 is G. In some embodiments, X_2 is S.

[324] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H2 comprising the amino acid sequence (X_1)ISHEG(X_2)(X_3)KYYADSVKG, wherein, optionally: X_1 is V or S; X_2 is S or G; and X_3 is F or L (SEQ ID NO: 393). In some embodiments, X_1 is a V. In some embodiment, X_1 is a S. In some embodiments, X_2 is S. In some embodiments, X_2 is G. In some embodiments, X_3 is F. In some embodiments, X_3 is L.

[325] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H3 comprising the amino acid sequence (X_1)(X_2)P(X_3)(X_4)(X_5)(X_6)RRGG(X_7)(X_8)(X_9), wherein, optionally: X_1 is A or V; X_2 is R, V, G or K; X_3 is R, H or L; X_4 is I, V or G; X_5 is A, S, or L; X_6 is A or V; X_7 is F or Y; X_8 is D, G, R, or S; and, X_9 is Y, G, R, L, V, A or K (SEQ ID NO: 394). In some embodiments, X_1 is A. In some embodiments, X_1 is V. In some embodiments, X_2 is R. In some embodiments, X_2 is V. In some embodiments, X_2 is G. In some embodiments, X_2 is K. In some

embodiments, X_3 is R. In some embodiments, X_3 is H. In some embodiments, X_3 is L. In some embodiments, X_4 is I. In some embodiments, X_4 is V. In some embodiments, X_4 is G. In some embodiments, X_5 is A. In some embodiments, X_5 is S. In some embodiments, X_5 is L. In some embodiments, X_6 is A. In some embodiments, X_6 is V. In some embodiments, X_7 is F. In some embodiments, X_7 is Y. In some embodiments, X_8 is D. In some embodiments, X_8 is G. In some embodiments, X_8 is R. In some embodiments, X_8 is S. In some embodiments, X_9 is Y. In some embodiments, X_9 is G. In some embodiments, X_9 is R. In some embodiments, X_9 is L. In some embodiments, X_9 is V. In some embodiments, X_9 is A. In some embodiments, X_9 is K.

[326] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises three heavy chain CDRs and three light chain CDRs, wherein the heavy chain CDRs comprise:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEG(X_2)(X_3)KYYADSVKG, wherein, optionally: X_1 is V or S; X_2 is S or G; and X_3 is F or L (SEQ ID NO: 393); and

c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)P(X_3)(X_4)(X_5)(X_6)RRGG(X_7)(X_8)(X_9), wherein, , optionally: X_1 is A or V; X_2 is R, V, G or K; X_3 is R, H or L; X_4 is I, V or G; X_5 is A, S, or L; X_6 is A or V; X_7 is F or Y; X_8 is D, G, R, or S; and, X_9 is Y, G, R, L, V, A or K (SEQ ID NO: 394).

[327] In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[328] In some embodiments, the antibody, or antigen-binding fragment, comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEG(X_2)(X_3)KYYADSVKG, wherein, optionally: X_1 is V or S; X_2 is S or G; and X_3 is F or L (SEQ ID NO: 393);

c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)P(X_3)(X_4)(X_5)(X_6)RRGG(X_7)(X_8)(X_9), wherein, optionally: X_1 is A or V; X_2 is R, V, G or K; X_3 is R, H or L; X_4 is I, V or G; X_5 is A, S, or L; X_6 is A or V; X_7 is F or Y; X_8 is D, G, R, or S; and, X_9 is Y, G, R, L, V, A or K (SEQ ID NO: 394);

d) CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes;

e) CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[329] In some embodiments, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

[330] In a particular embodiment, the antibody, or antigen-binding fragment, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3; wherein the antibody is a fully human or humanized antibody or a fragment thereof, wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEG(X_2)(X_3)KYYADSVKG, wherein, optionally: X_1 is V or S; X_2 is S or G; and X_3 is F or L (SEQ ID NO: 393);

c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)P(X_3)(X_4)(X_5)(X_6)RRGG(X_7)(X_8)(X_9), wherein, optionally: X_1 is A or V; X_2 is R, V, G or K; X_3 is R, H or L; X_4 is I, V or G; X_5 is A, S, or L; X_6 is A or V; X_7 is F or Y; X_8 is D, G, R, or S; and, X_9 is Y, G, R, L, V, A or K (SEQ ID NO: 394);

d) CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes;

e) CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[331] In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured in a

suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[332] In another embodiment, such antibody is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, such antibody is also cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[333] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is also isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

[334] In another aspect, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392). In some embodiments, X_1 is S. In some embodiments, X_1 is R. In some embodiments, X_2 is G. In some embodiments, X_2 is S.

[335] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H2 comprising the amino acid sequence (X_1)ISHEGS(X_2)KYYADSVKG, wherein, optionally: X_1 is V or S; and, X_2 is F or L (SEQ ID NO: 382). In some embodiments, X_1 is a V. In some embodiment, X_1 is a S. In some embodiments, X_3 is F. In some embodiments, X_3 is L.

[336] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H3 comprising the amino acid sequence A(X_1)PRI(X_2)ARRGGFGY, wherein, optionally: X_1 is R or V; X_2 is A or L (SEQ ID NO: 383). In some embodiments, X_1 is R. In some embodiments, X_1 is V. In some embodiments, X_2 is A. In some embodiments, X_2 is L.

[337] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises three heavy chain CDRs and three light chain CDRs, wherein the heavy chain CDRs comprise:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEGS(X_2)KYYADSVKG, wherein, optionally: X_1 is V or S; and, X_2 is F or L (SEQ ID NO: 382); and

c) CDR-H3 comprising the amino acid sequence A(X_1)PRI(X_2)ARRGGFGY, wherein, optionally: X_1 is R or V; X_2 is A or L (SEQ ID NO: 383).

[338] In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes. In some embodiment, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[339] In some embodiments, the antibody, or antigen-binding fragment, comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEGS(X_2)KYYADSVKG, wherein, optionally: X_1 is V or S; and, X_2 is F or L (SEQ ID NO: 382);

c) CDR- comprising the amino acid sequence A(X_1)PRI(X_2)ARRGGFGY, wherein, optionally: X_1 is R or V; X_2 is A or L (SEQ ID NO: 383);

d) CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes;

e) CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[340] In some embodiments, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

[341] In a particular embodiment, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3; wherein the antibody is a fully human or humanized antibody or a fragment thereof, wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEGS(X_2)KYYADSVKG, wherein: X_1 is V or S; and, X_2 is F or L (SEQ ID NO: 382);

c) CDR-H3 comprising the amino acid sequence A(X_1)PRI(X_2)ARRGGFGY, wherein, optionally: X_1 is R or V; X_2 is A or L (SEQ ID NO: 383);

d) CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes;

e) CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

[342] In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer

Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[343] In another embodiment, such antibody is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, such antibody is also cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[344] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is also isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

[345] In another aspect, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:100, with the proviso that the serine residue at position 4 of SEQ ID NO:100 may be substituted with a histidine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:100, with the proviso that the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:100, with the proviso that the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine. SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400.

[346] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:100, with the proviso that (i) the serine residue at position 4 of SEQ ID NO:100 may

be substituted with a histidine; (ii) the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine; and/or, (iii) the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine. SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400.

[347] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:101, with the proviso that the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:101, with the proviso that the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine. In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:101, with the proviso that the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine. SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401.

[348] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1: SEQ ID NO:101, with the proviso that (i) the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine; (ii) the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine; and/or, (iii) the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine. SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401.

[349] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises three heavy chain CDRs and three light chain CDRs, wherein the heavy chain CDRs comprise:

a) CDR-H1: SEQ ID NO:100 (SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400), with the proviso that:
   i. the serine residue at position 4 of SEQ ID NO:100 may be substituted with a histidine;
   ii. the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine; and/or,
   iii. the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine;

b) CDR-H2: SEQ ID NO:101 (SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401), with the proviso that:
   i. the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine;
   ii. the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine; and/or,

iii. the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine; and

c) CDR-H3: SEQ ID NO:102, optionally comprising up to three, four, five or six amino acid changes.

[350] In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L1 as set forth in SEQ ID NO:103, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L2 as set forth in SEQ ID NO:104, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L3 as set forth in SEQ ID NO:105, optionally comprising one or more amino acid changes.

[351] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:100 (SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400), with the proviso that:

i. the serine residue at position 4 of SEQ ID NO:100 may be substituted with a histidine;

ii. the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine; and/or,

iii. the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine;

b) CDR-H2: SEQ ID NO:101 (SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401), with the proviso that:

i. the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine;

ii. the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine; and/or,

iii. the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine; and

c) CDR-H3: SEQ ID NO:102, optionally comprising one or more amino acid changes.

d) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;

e) CDR-L2: SEQ ID NO:104, optionally comprising one or more amino acid changes; and,

f) CDR-L3: SEQ ID NO:105, optionally comprising one or more amino acid changes.

[352] In some embodiments, the antibody, or antigen-binding fragment, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment

thereof, does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

[353] In a particular embodiment, the antibody, or antigen-binding fragment, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3; wherein the antibody is a fully human or humanized antibody or a fragment thereof, wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:100 (SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400), with the proviso that:
   i. the serine residue at position 4 of SEQ ID NO:100 may be substituted with a histidine;
   ii. the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine; and/or,
   iii. the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine;
b) CDR-H2: SEQ ID NO:101 (SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401), with the proviso that:
   i. the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine;
   ii. the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine; and/or,
   iii. the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine;
c) CDR-H3: SEQ ID NO:102, optionally comprising one or more amino acid changes;
d) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;
e) CDR-L2: SEQ ID NO:104, optionally comprising one or more amino acid changes; and,
f) CDR-L3: SEQ ID NO:105, optionally comprising one or more amino acid changes.

[354] In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some

embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[355] In another embodiment, such antibody is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, such antibody is also cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[356] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is also isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

[357] In another aspect, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S or P; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 395). In some embodiments, X_1 is a S. In some embodiments, X_1 is P. In some embodiments, X_2 is S. In some embodiments, X_2 is H. In some embodiments, X_2 is R. In some embodiments, X_3 is S. In some embodiments, X_3 is G. In some embodiments, X_4 is G. In some embodiments, X_4 is I. In some embodiments, X_4 is N. In some embodiments, X_4 is V.

[358] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally, X_1 is S or T (SEQ ID NO: 396). In some embodiments, X_1 is a S. In some embodiment, X_1 is a T.

[359] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H3 comprising the amino acid sequence (X_1)(X_2)D(X_3)(X_4)Y(X_5)(X_6)(X_7)(X_8)G(X_9)(X_{10})(X_{11}), wherein, optionally: X_1 is A or V; X_2 is R, S or G, X_3 is P, Y, R, V, I, H, T or E; X_4 is S, D, E or N; X_5 is D, A or T; X_6 is S, G, T or A; X_7 is I, A, R, Q, or V; X_8 is A, E, K, G or T; X_9 is M or I; X_{10} is D, L, Q, V, N or G;

and, X_{11} is V, R, N, E or K (SEQ ID NO: 397). In some embodiments, X_1 is A. In some embodiments, X_1 is V. In some embodiments, X_2 is R. In some embodiments, X_2 is S. In some embodiments, X_2 is G. In some embodiments, X_3 is P. In some embodiments, X_3 is Y. In some embodiments, X_3 is R. In some embodiments, X_3 is V. In some embodiments, X_3 is I. In some embodiments, X_3 is H. In some embodiments, X_3 is T. In some embodiments, X_3 is E. In some embodiments, X_4 is S. In some embodiments, X_4 is D. In some embodiments, X_4 is E. In some embodiments, X_4 is N. In some embodiments, X_5 is D. In some embodiments, X_5 is A. In some embodiments, X_5 is T. In some embodiments, X_6 is S. In some embodiments, X_6 is G. In some embodiments, X_6 is T. In some embodiments, X_6 is A. In some embodiments, X_7 is I. In some embodiments, X_7 is A. In some embodiments, X_7 is R. In some embodiments, X_7 is Q. In some embodiments, X_7 is V. In some embodiments, X_8 is A. In some embodiments, X_8 is E. In some embodiments, X_8 is K. In some embodiments, X_8 is G. In some embodiments, X_8 is T. In some embodiments, X_9 is M. In some embodiments, X_9 is I. In some embodiments, X_{10} is D. In some embodiments, X_{10} is L. In some embodiments, X_{10} is Q. In some embodiments, X_{10} is V. In some embodiments, X_{10} is N. In some embodiments, X_{10} is G. In some embodiments, X_{11} is V. In some embodiments, X_{11} is R. In some embodiments, X_{11} is N. In some embodiments, X_{11} is E. In some embodiments, X_{11} is K.

[360] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises three heavy chain CDRs and three light chain CDRs, wherein the heavy chain CDRs comprise:

a) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S or P; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 395);

b) CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally, X_1 is S or T (SEQ ID NO: 396); and

c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)D(X_3)(X_4)Y(X_5)(X_6)(X_7)(X_8)G(X_9)(X_{10})(X_{11}), wherein, optionally: X_1 is A or V; X_2 is R, S or G, X_3 is P, Y, R, V, I, H, T or E; X_4 is S, D, E or N; X_5 is D, A or T; X_6 is S, G, T or A; X_7 is I, A, R, Q, or V; X_8 is A, E, K, G or T; X_9 is M or I; X_{10} is D, L, Q, V, N or G; and, X_{11} is V, R, N, E or K (SEQ ID NO: 397).

[361] In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L1 as set forth in SEQ ID NO:103, optionally comprising one or more amino acid changes. In some embodiment, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L2 as set forth in SEQ ID NO:104, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L3 as set forth in SEQ ID NO:105, optionally comprising one or more amino acid changes.

[362] In some embodiments, the antibody, or antigen-binding fragment, comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S or P; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 395);
b) CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally, X_1 is S or T (SEQ ID NO: 396);
c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)D(X_3)(X_4)Y(X_5)(X_6)(X_7)(X_8)G(X_9)(X_{10})(X_{11}), wherein, optionally: X_1 is A or V; X_2 is R, S or G, X_3 is P, Y, R, V, I, H, T or E; X_4 is S, D, E or N; X_5 is D, A or T; X_6 is S, G, T or A; X_7 is I, A, R, Q, or V; X_8 is A, E, K, G or T; X_9 is M or I; X_{10} is D, L, Q, V, N or G; and, X_{11} is V, R, N, E or K (SEQ ID NO: 397);
d) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;
e) CDR-L2: SEQ ID NO: 104, optionally comprising one or more amino acid changes; and
f) CDR-L3: SEQ ID NO: 105, optionally comprising one or more amino acid changes.

[363] In some embodiments, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

[364] In a particular embodiment, the antibody, or antigen-binding fragment, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3; wherein the antibody is a fully human or humanized antibody or a fragment thereof, wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S or P; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 395);
b) CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally, X_1 is S or T (SEQ ID NO: 396);
c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)D(X_3)(X_4)Y(X_5)(X_6)(X_7)(X_8)G(X_9)(X_{10})(X_{11}), wherein, optionally: X_1 is A or V; X_2 is R, S or G, X_3 is P, Y, R, V, I, H, T or E; X_4 is S, D, E or N; X_5 is D, A or T; X_6 is S, G, T or A; X_7 is I, A, R, Q, or V; X_8 is A, E, K, G or T; X_9 is M or I; X_{10} is D, L, Q, V, N or G; and, X_{11} is V, R, N, E or K (SEQ ID NO: 397);
d) CDR-L1 as set forth in SEQ ID NO:103, optionally comprising one or more amino acid changes;
e) CDR-L2 as set forth in SEQ ID NO: 104, optionally comprising one or more amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO: 105, optionally comprising one or more amino acid changes.

[365] In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[366] In another embodiment, such antibody is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, such antibody is also cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[367] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is also isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

[368] In another aspect, the antibody, or antigen-binding fragment thereof, comprises a CDR-H1 comprising the amino acid $G(X_1)I(X_2)SSSYYW(X_3)$, wherein, optionally: X_1 is S or P; X_2 is H or R; and, X_3 is G, I or N (SEQ ID NO: 384). In some embodiments, X_1 is a S. In some embodiments, X_1 is a P. In some embodiments, X_2 is a H. In some embodiments, X_2 is an R. In some embodiments, X_3 is a G. In some embodiments, X_3 is an I. In some embodiments, X_3 is an N.

[369] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H2 comprising the amino acid sequence $SISYSA(X_1)TYYYNPSLKS$, wherein, optionally, X_1 is S or T (SEQ ID NO: 396). In some embodiments, X_1 is a S. In some embodiment, X_1 is a T.

[370] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises a CDR-H3 comprising the amino acid sequence $A(X_1)D(X_2)SYD(X_3)(X_4)AGM(X_5)(X_6)$, wherein, optionally: X_1 is R, S or G, X_2 is P or V; X_3 is S or A; X_4 is A, R, I or V; X_5 D, Q, or G; and, X_6 is V or R (SEQ ID NO: 385). In some embodiments, X_1 is R. In some embodiments, X_1 is S. In some embodiments, X_1 is G. In some embodiments, X_2 is P. In some embodiments, X_2 is V. In some embodiments, X_3 is S. In some embodiments, X_3 is A. In some embodiments, X_4 is A. In some embodiments, X_4 is R. In some embodiments, X_4 is I. In some embodiments, X_4 is V. In some embodiments, X_5 is D. In some embodiments, X_5 is Q. In some embodiments, X_5 is G. In some embodiments, X_6 is V. In some embodiments, X_6 is R.

[371] In some embodiments, the antibody, or antigen-binding fragment thereof, comprises three heavy chain CDRs and three light chain CDRs, wherein the heavy chain CDRs comprise:

a) CDR-H1 comprising the amino acid sequence $G(X_1)I(X_2)SSSYYW(X_3)$, wherein, optionally: X_1 is S or P; X_2 is H or R; and, X_3 is G, I or N (SEQ ID NO: 384);
b) CDR-H2 comprising the amino acid sequence $SISYSA(X_1)TYYYNPSLKS$, wherein, optionally, X_1 is S or T (SEQ ID NO: 396); and
c) CDR-H3 comprising the amino acid sequence $A(X_1)D(X_2)SYD(X_3)(X_4)AGM(X_5)(X_6)$, wherein, optionally: X_1 is R, S or G, X_2 is P or V; X_3 is S or A; X_4 is A, R, I or V; X_5 D, Q, or G; and, X_6 is V or R (SEQ ID NO: 385).

[372] In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L1 as set forth in SEQ ID NO:103, optionally comprising one or more amino acid changes. In some embodiment, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L2 as set forth in SEQ ID NO:104, optionally comprising one or more amino acid changes. In some embodiments, the antibody, or antigen-binding fragment thereof, further comprises a CDR-L3 as set forth in SEQ ID NO:105, optionally comprising one or more amino acid changes.

[373] In some embodiments, the antibody, or antigen-binding fragment, comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence $G(X_1)I(X_2)SSSYYW(X_3)$, wherein, optionally: X_1 is S or P; X_2 is H or R; and, X_3 is G, I or N (SEQ ID NO: 384);

b) CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally, X_1 is S or T (SEQ ID NO: 396);
c) CDR-H3 comprising the amino acid sequence A(X_1)D(X_2)SYD(X_3)(X_4)AGM(X_5)(X_6), wherein, optionally: X_1 is R, S or G, X_2 is P or V; X_3 is S or A; X_4 is A, R, I or V; X_5 D, Q, or G; and, X_6 is V or R (SEQ ID NO: 385);
d) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;
e) CDR-L2: SEQ ID NO: 104, optionally comprising one or more amino acid changes; and
f) CDR-L3: SEQ ID NO: 105, optionally comprising one or more amino acid changes.

[374] In some embodiments, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind a human GARP-proTGFβ1 complex. In some embodiments, the antibody, or antigen-binding fragment thereof, does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

[375] In a particular embodiment, the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-proTGFβ1 complex, and does not bind a human GARP-proTGFβ1 complex; wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3; wherein the antibody is a fully human or humanized antibody or a fragment thereof, wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)SSSYYW(X_3), wherein, optionally: X_1 is S or P; X_2 is H or R; and, X_3 is G, I or N (SEQ ID NO: 384);
b) CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally, X_1 is S or T (SEQ ID NO: 396);
c) CDR-H3 comprising the amino acid sequence A(X_1)D(X_2)SYD(X_3)(X_4)AGM(X_5)(X_6), wherein, optionally: X_1 is R, S or G, X_2 is P or V; X_3 is S or A; X_4 is A, R, I or V; X_5 D, Q, or G; and, X_6 is V or R (SEQ ID NO: 385);
d) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;
e) CDR-L2: SEQ ID NO: 104, optionally comprising one or more amino acid changes; and
f) CDR-L3: SEQ ID NO: 105, optionally comprising one or more amino acid changes.

[376] In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer

Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a human LTBP1-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, such antibody binds a human LTBP3-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[377] In another embodiment, such antibody is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, such antibody is also cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 100 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 50 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 25 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI). In some embodiments, such antibody binds a mouse LTBP1-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI); and/or, the antibody binds a mouse LTBP3-proTGFβ1 complex with a KD of < 10 nM as measured in a suitable in vitro binding assay such as Bio-Layer Interferometry (BLI).

[378] In another embodiment, such antibody does not bind to human GARP-proTGFβ1. In preferred embodiments, such context-selective antibody is also isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

[379] Also provided herein are antibodies, or antigen-binding fragments thereof, which binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with yet higher affinities and further advantageous combinations of binding properties.

[380] Accordingly, in one aspect, the antibody, or antigen-binding fragment thereof, comprises the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTFRSYVMH (SEQ ID NO: 166);

b) CDR-H2 comprising the amino acid sequence VISHEGS(X_1)KYYADSVKG, wherein: X_1 is L or G (SEQ ID NO: 366); and

c) CDR-H3 comprising the amino acid sequence A(X_1)PRIAARRGGFG(X_2), wherein: X_1 is V, R or L; and X_2 is Y, S or T (SEQ ID NO: 367);

d) CDR-L1 comprising the amino acid sequence TRS(X_1)G(X_2)ID(X_3)NYVQ, wherein, X_1 is S or H; X_2 is N, L, S or A; and X_3 is N, D or Y (SEQ ID NO: 368);

e) CDR-L2 comprising the amino acid sequence ED(X_1)(X_2)RPS, wherein: X_1 is N, F or A; and X_2 is Q, I or V (SEQ ID NO: 369); and

f) CDR-L3 comprising the amino acid sequence Q(X_1)YD(X_2)(X_3)(X_4)Q(X_5)VV, wherein: X_1 is S or G; X_2 is S, F, Y, D, H or W; X_3 is N, D or S; X_4 is N, A, L, E or T; and X_5 is G, R, A or L (SEQ ID NO: 370).

[381] In some embodiments, within CDR-H3: X_1 is R or L. Within CDR-L3: X_2 may be Y. Within CDR-L3: X_3 may be D; and X_4 may be T. In some preferred embodiments, within CDR-H3: X_1 is R or L (optionally R), within CDR-L3: X_2 is Y; and within CDR-L3: X_3 is D; and X_4 is T.

[382] In alternative embodiments, within CDR-H3: X_1 is R or L (optionally R), within CDR-L3: X_2 is Y and within CDR-L3: X_3 is D; X_4 is N; and X_5 is A.

[383] In some embodiments within CDR-L1: X_1 is S or H; X_2 is N or A; and X_3 is N, D or Y; within CDR-L2: X_1 is N or F; and X_2 is Q or V; and within CDR-L3: X_1 is S or G; X_2 is S, Y, D or W; X_3 is D or S; X_4 is N, L or T; and X_5 is G, R, A or L. In some embodiments, within CDR-L1: X_1 is S; X_2 is N; and X_3 is N or Y; within CDR-L2: X_1 is N; and X_2 is Q or V; and within CDR-L3: X_1 is S or G; X_2 is S, Y or W; X_3 is D; X_4 is N or T; and X_5 is G, R or A. In some embodiments, within CDR-L3: X_1 is S; X_2 is S or Y; X_3 is D; X_4 is N or T; and X_5 is G, R or A. In some embodiments, within CDR-L3: X_1 is S; X_2 is Y; X_3 is D; X_4 is N or T; and X_5 is G or A. In some preferred embodiments, within CDR-L3: X_1 is S; X_2 is Y; X_3 is D; X_4 is T; and X_5 is G.

[384] In particularly preferred embodiments, the antibody or antigen-binding fragment has the CDRs of Ab42, *e.g.*: CDR-H1 comprising the amino acid sequence FTFRSYVMH (SEQ ID NO: 166); CDR-H2 comprising the amino acid sequence VISHEGSLKYYADSVKG (SEQ ID NO: 167); CDR-H3 comprising the amino acid sequence ARPRIAARRGGFGY (SEQ ID NO: 168); CDR-L1 comprising the amino acid sequence TRSSGNIDNNYVQ (SEQ ID NO: 169); CDR-L2 comprising the amino acid sequence EDNQRPS (SEQ ID NO: 170); and CDR-L3 comprising the amino acid sequence QSYDYDTQGVV (SEQ ID NO: 171).

[385] In some embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 318; and a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 319.

[386] In some embodiments, the antibody, or antigen-binding fragment, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by suitable in vitro binding assay, such as BLI. For example, the antibody, or antigen-binding fragment, may bind a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by suitable in vitro binding assay, such as BLI. In some embodiments, the antibody, or antigen-binding fragment, binds the human LTBP1- and/or LTBP3-proTGFβ1 complex with a K_D of < 1 nM as measured by suitable in vitro binding assay, such as BLI.

[387] In some embodiments, the antibody, or antigen-binding fragment thereof does not show detectable binding to a human GARP-proTGFβ1 complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and/or human LTBP3-TGFβ1. For example, the antibody, or antigen-binding fragment may not show detectable binding to a human GARP-proTGFβ1 complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and human LTBP3-TGFβ1 complex.

[388] In some embodiments, the antibody, or antigen-binding fragment thereof, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower (*e.g.,* at least 75 times lower, at least 100 times lower) than the K_D when binding to a human GARP-proTGFβ1 complex under the same assay conditions. For example, the antibody, or antigen-binding fragment thereof, may bind a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower (*e.g.,* at least 75 times lower, at least 100 times lower) than the K_D when binding to a human GARP-proTGFβ1 complex under the same assay conditions. In some embodiments, K_D is as determined by BLI or SPR. In some embodiments, K_D is as determined by SPR.

[389] In some embodiments, the antibody, or antigen-binding fragment thereof does not show detectable binding to an LRRC33-proTGFβ1 latent complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and/or human LTBP3-TGFβ1. For example, the antibody, or antigen-binding fragment thereof may not show detectable binding to an LRRC33-proTGFβ1 latent complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and human LTBP3-TGFβ1.

[390] In some embodiments, the antibody, or antigen-binding fragment thereof, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower (*e.g.,* at least 75 times lower, at least 100 times lower) than the K_D when binding to a human LRRC33-proTGFβ1 complex under the same assay conditions. For example, the antibody, or antigen-binding fragment thereof, may bind a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower (*e.g.,* at least 75 times lower, at least 100 times lower) than the K_D when binding to a human LRRC33-proTGFβ1 complex under the same assay conditions. In some embodiments, K_D is as determined by BLI or SPR. In some embodiments, K_D is as determined by SPR.

[391] In some embodiments, the antibody, or antigen-binding fragment thereof, is cross-reactive with mouse LTBP1-proTGFβ1. In some embodiments, the antibody, or antigen-binding fragment thereof, is cross-reactive with mouse LTBP3-proTGFβ1. In some embodiments, the antibody, or antigen-binding fragment thereof, binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured by BLI. In some embodiments, the antibody, or antigen-binding fragment thereof, binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured by BLI.

[392] In further embodiments, the antibody which selectively binds a human LTBP1-TGFβ1 complex and/or a human LTBP3-TGFβ1 complex may not show meaningful binding (*e.g.,* may not show a response

of more than 0.1 units (nm)) on exposure to a human GARP-proTGFβ1 complex in a BLI assay (*e.g.,* Octet) when the human GARP-proTGFβ1 complex is at a concentration of 200nM.

[393] In another aspect, the antibody, or antigen-binding fragment thereof, comprises the following six CDRs:

a) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 386);

b) CDR-H2 comprising the amino acid sequence SISYS(X_1)(X_2)TYY, wherein, optionally: X_1 is G or A; and X_2 is S or T (SEQ ID NO: 398);

c) CDR-H3 comprising the amino acid sequence A(X_1)DPSYDS(X_2)AGM(X_3)V, wherein, optionally: X_1 is R, S or G; X_2 is A or I; and X_3 is D or Q (SEQ ID NO: 387);

d) CDR-L1 comprising the amino acid sequence RAS(X_1)(X_2)IS(X_3)YLN, wherein, optionally: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y (SEQ ID NO: 389);

e) CDR-L2 comprising the amino acid sequence (X_1)AS(X_2)(X_3)QS, wherein, optionally: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R (SEQ ID NO: 390);

f) CDR-L3 comprising the amino acid sequence QQ(X_1)(X_2)D(X_3)P(X_4)T, wherein, optionally: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L (SEQ ID NO: 391).

[394] In some embodiments: within CDR-H1: X_1 is S; X_2 is S or R; X_3 is S; and, X_4 is G; within CDR-H2: X_1 is G or A; and X_2 is S or T; within CDR-H3: X_1 is R, S or G; X_2 is A or I; and X_3 is D or Q; within CDR-L1: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y; within CDR-L2: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R; and within CDR-L3: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L.

[395] In some embodiments: CDR-H1 comprises the amino acid sequence GSIRSSSYYWG (SEQ ID NO: 292); CDR-H2 comprises the amino acid sequence SISYSATTYY (SEQ ID NO: 293); within CDR-H3: X_1 is S or G; X_2 is A or I; and X_3 is D or Q; within CDR-L1: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y; within CDR-L2: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R; and within CDR-L3: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L.

[396] In some embodiments: CDR-H1 comprises the amino acid sequence GSIRSSSYYWG (SEQ ID NO: 292); CDR-H2 comprises the amino acid sequence SISYSATTYY (SEQ ID NO: 293); CDR-H3 comprises the amino acid sequence AGDPSYDSIAGMQV (SEQ ID NO: 294); CDR-L1 comprises the amino acid sequence RASQSISSYLN (SEQ ID NO: 295); CDR-L2 comprises the amino acid sequence AASNLQS (SEQ ID NO: 296); and CDR-L3 comprises the amino acid sequence QQSFDWPLT (SEQ ID NO: 297).

[397] In some embodiments, the antibody or antigen-binding fragment comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 360; and a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 361.

[398] In some embodiments, the antibody, or antigen-binding fragment, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by suitable in vitro binding assay, such as BLI. For example, the antibody, or antigen-binding fragment, may bind a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by suitable in vitro binding assay, such as BLI. In some embodiments, the antibody, or antigen-binding fragment, binds the human LTBP1- and/or LTBP3-proTGFβ1 complex with a K_D of < 1 nM as measured by suitable in vitro binding assay, such as BLI.

[399] In some embodiments, the antibody, or antigen-binding fragment thereof does not show detectable binding to a human GARP-proTGFβ1 complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and/or human LTBP3-TGFβ1. For example, the antibody, or antigen-binding fragment may not show detectable binding to a human GARP-proTGFβ1 complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and human LTBP3-TGFβ1 complex.

[400] In some embodiments, the antibody, or antigen-binding fragment thereof, binds a human LTBP1-proTGFβ1 complex and/or a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower (*e.g.,* at least 75 times lower, at least 100 times lower) than the K_D when binding to a human GARP-proTGFβ1 complex under the same assay conditions. For example, the antibody, or antigen-binding fragment thereof, may bind a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D that is at least 50 times lower (*e.g.,* at least 75 times lower, at least 100 times lower) than the K_D when binding to a human GARP-proTGFβ1 complex under the same assay conditions. In some embodiments, K_D is as determined by BLI or SPR. In some embodiments, K_D is as determined by SPR.

[401] In some embodiments, the antibody, or antigen-binding fragment thereof does not show detectable binding to an LRRC33-proTGFβ1 latent complex, as measured by BLI, under the same assay conditions as used to measure binding to human LTBP1-proTGFβ1 complex and/or human

pro-MMP-9. KLK2 activates latent TGFβ1, rendering prostate cancer adjacent to fibroblasts permissive to cancer growth. KLK3 has been widely studied as a diagnostic marker for prostate cancer (PSA). KLK3 may directly activate TGFβ1 by processing plasminogen into plasmin, which proteolytically cleaves LAP. KLK6 may be a potential marker for Alzheimer's disease.

[573] Known activators of TGFβ1, such as plasmin, TSP-1 and αVβ6 integrin, all interact directly with LAP. It is postulated that proteolytic cleavage of LAP may destabilize the LAP-TGFβ interaction, thereby releasing active TGFβ1. It has been suggested that the region containing 54-LSKLRL-59 (SEQ ID NO: 388) is important for maintaining TGFβ1 latency. Thus, agents (*e.g.,* antibodies) that stabilize the interaction, or block the proteolytic cleavage of LAP may prevent TGFβ activation.

[574] Many of these proteases associated with pathological conditions (*e.g.,* cancer) function through distinct mechanisms of action. Thus, targeted inhibition of particular proteases, or combinations of proteases, may provide therapeutic benefits for the treatment of conditions involving the protease-TGFβ axis. Accordingly, it is contemplated that inhibitors (*e.g.,* TGFβ1 antibodies) that selectively inhibit protease-induced activation of TGFβ1 may be advantageous in the treatment of such diseases (*e.g.,* cancer). Similarly, selective inhibition of TGFβ1 activation by one protease over another protease may also be preferred, depending on the condition being treated.

[575] Plasmin is a serine protease produced as a precursor form called Plasminogen. Upon release, Plasmin enters circulation and therefore is detected in serum. Elevated levels of Plasmin appear to correlate with cancer progression, possibly through mechanisms involving disruption of the extracellular matrix (*e.g.,* basement membrane and stromal barriers) which facilitates tumor cell motility, invasion, and metastasis. Plasmin may also affect adhesion, proliferation, apoptosis, cancer nutrition, oxygen supply, formation of blood vessels, and activation of VEGF (Didiasova *et al.*, *Int. J. Mol. Sci*, 2014, 15, 21229-21252). In addition, Plasmin may promote the migration of macrophages into the tumor microenvironment (Philips et al., *Cancer Res.* 2011 Nov 1;71(21):6676-83 and Choong et al., *Clin. Orthop. Relat. Res.* 2003, *415S*, S46-S58). Indeed, tumor-associated macrophages (TAMs) are well characterized drivers of tumorigenesis through their ability to promote tumor growth, invasion, metastasis, and angiogenesis.

[576] Plasmin activities have been primarily tied to the disruption of the ECM. However, there is mounting evidence that Plasmin also regulate downstream MMP and TGF beta activation. Specifically, Plasmin has been suggested to cause activation of TGF beta through proteolytic cleavage of the Latency Associated Peptide (LAP), which is derived from the N-terminal region of the TGF beta gene product (Horiguchi et al., *J Biochem.* 2012 Oct; 152(4):321-9), resulting in the release of active growth factor. Since TGFβ1 may promote cancer progression, this raises the possibility that plasmin-induced activation of TGFb may at least in part mediate this process.

Embodiments

The present invention encompasses various embodiments. Non-limiting examples are listed below:

1. An antibody, or antigen-binding fragment thereof, comprising at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:94 (SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399), with the proviso that, optionally:

i. the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine;

ii. the asparagine residue at position 4 of SEQ ID NO:94 may be substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine;

iii. the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine;

iv. the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine;

v. the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine;

vi. the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine; and/or,

vii. the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine;

b) CDR-H2: SEQ ID NO:95, optionally comprising one or more amino acid changes;

c) CDR-H3: SEQ ID NO:96, optionally comprising one or more amino acid changes;

d) CDR-L1: SEQ ID NO:97, optionally comprising one or more amino acid changes;

e) CDR-L2: SEQ ID NO:98, optionally comprising one or more amino acid changes; and,

f) CDR-L3: SEQ ID NO:99, optionally comprising one or more amino acid changes.

2. The antibody, or antigen-binding fragment thereof, according to embodiment 1, comprising at least three of the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein, optionally: X_1 is S or R; and X_2 is G or S (SEQ ID NO: 392);

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEG(X_2)(X_3)KYYADSVKG, wherein, optionally: X_1 is V or S; X_2 is S or G; and X_3 is F or L (SEQ ID NO: 393); and

c) CDR-H3 comprising the amino acid sequence (X_1)(X_2)P(X_3)(X_4)(X_5)(X_6)RRGG(X_7)(X_8)(X_9), wherein, optionally: X_1 is A or V; X_2 is R, V, G or K; X_3 is R, H or L; X_4 is I, V or G; X_5 is A, S, or L; X_6 is A or V; X_7 is F or Y; X_8 is D, G, R, or S; and, X_9 is Y, G, R, L, V, A or K (SEQ ID NO: 394).

d) CDR-L1 as set forth in SEQ ID NO:97, optionally comprising one or more amino acid changes;

e) CDR-L2 as set forth in SEQ ID NO:98, optionally comprising one or more amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO:99, optionally comprising one or more amino acid changes.

3. The antibody, or antigen-binding fragment thereof, according to embodiment 2, wherein:

a) within CDR-H2; X_2 is S; and

b) within CDR-H3; X_1 is A; X_2 is R or V; X_3 is R; X_4 is I; X_5 is A or L; X_6 is A; X_7 is F; X_8 is G; and X_9 and Y.

3.1 The antibody, or antigen-binding fragment thereof, according to embodiment 3, wherein one or more of the CDR-L1, CDR-L2, and CDR-L3 is/are affinity matured and/or optimized by CDR diversification and/or mutagenesis.

4. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: SEQ ID NO: 88; and/or,

wherein the antibody comprises a variable light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 89.

5. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, comprising:

a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 88; and

a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 89.

6. An antibody, or antigen-binding fragment thereof, comprising at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:100 (SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400), with the proviso that, optionally:

i. the serine residue at position 4 of SEQ ID NO:100 may be substituted with a histidine;

ii. the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine; and/or,

iii. the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine;

b) CDR-H2: SEQ ID NO:101 (SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401), with the proviso that, optionally:

i. the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine;

ii. the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine; and/or,

iii. the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine;

c) CDR-H3: SEQ ID NO:102, optionally comprising one or more amino acid changes;

d) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;

e) CDR-L2: SEQ ID NO:104, optionally comprising one or more amino acid changes; and,

f) CDR-L3: SEQ ID NO:105, optionally comprising one or more amino acid changes.

7. The antibody, or antigen-binding fragment thereof, according to embodiment 6, comprising at least three of the following six CDRs:

g) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S or P; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 395);

h) CDR-H2 comprising the amino acid sequence SISYSA(X_1)TYYNPSLKS, wherein, optionally: X_1 is S or T (SEQ ID NO: 396);

i) CDR-H3 comprising the amino acid sequence (X_1)(X_2)D(X_3)(X_4)Y(X_5)(X_6)(X_7)(X_8)G(X_9) (X_{10})(X_{11}), wherein, optionally: X_1 is A or V; X_2 is R, S or G, X_3 is P, Y, R, V, I, H, T or E; X_4 is S, D, E or N; X_5 is D, A or T; X_6 is S, G, T or A; X_7 is I, A, R, Q, or V; X_8 is A, E, K, G or T; X_9 is M or I; X_{10} is D, L, Q, V, N or G; and, X_{11} is V, R, N, E or K (SEQ ID NO: 397);

j) CDR-L1: SEQ ID NO:103, optionally comprising one or more amino acid changes;

k) CDR-L2: SEQ ID NO: 104, optionally comprising one or more amino acid changes; and

l) CDR-L3: SEQ ID NO: 105, optionally comprising one or more amino acid changes.

8. The antibody, or antigen-binding fragment thereof, according to embodiment 7, wherein:

g) within CDR-H1: X_2 is H or R; X_3 is S; and, X_4 is G, I or N; and

h) within CDR-H3: X_1 is A; X_3 is P or V; X_4 is S; X_5 is D; X_6 is S or A; X_7 is A, R, I or V; X_8 is A; X_9 is M; X_{10} is D, Q, or G; and, X_{11} is V or R.

8.1 The antibody, or antigen-binding fragment thereof, according to embodiment 8, wherein one or more of the CDR-L1, CDR-L2, and CDR-L3 is/are affinity matured and/or optimized by CDR diversification and/or mutagenesis.

9. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 6-8.1, comprising at least three CDRs selected from the following, optionally comprising one or more amino acid changes for each of the CDRs:

CDR-H1: SEQ ID NO:100;
CDR-H2: SEQ ID NO:101;
CDR-H3: SEQ ID NO:102;
CDR-L1: SEQ ID NO:103;
CDR-L2: SEQ ID NO:104; and,
CDR-L3: SEQ ID NO:105.

10. The antibody, or antigen-binding fragment thereof, according to one of embodiments 6-9, comprising a variable heavy chain region and a variable light chain region, wherein:

i) the variable heavy chain region comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: SEQ ID NO: 106; and/or,

ii) the variable light chain variable region comprises an amino acid sequence that is at least 90% identical to SEQ ID NO: 107.

11. The antibody, or antigen-binding fragment thereof, according to one of embodiments 6-9, wherein the antibody or antigen-binding portion thereof, comprises:

i) a variable heavy chain region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 106; and,

ii) a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 107.

12. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, comprising all six CDRs.

12.1 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises one amino acid change.

12.2 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises up to two amino acid changes.

12.3 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises up to three amino acid changes.

12.4 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises up to four amino acid changes.

12.5 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises up to five amino acid changes.

12.6 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises up to six amino acid changes.

12.7 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the one or more amino acid changes comprises up to seven amino acid changes.

12.8 The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein any one of the CDRs comprise no amino acid changes.

13. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP1-proTGFβ complex.

14. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, specifically binds a human LTBP3-proTGFβ complex.

15. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, does not bind a human GARP-proTGFβ complex.

16. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, specifically binds a human

LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ complex.

17. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3.

18. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, is a fully human or humanized antibody.

19. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, is an isolated antibody, or antigen-binding fragment thereof.

20. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, does not compete with any one of the antibodies SR-Ab1, SR-Ab2 or SR-Ab13 for binding to a human LTBP1-proTGFβ1 complex.

21. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, does not compete with any one of the antibodies SR-Ab1, SR-Ab2 or SR-Ab10 for binding to a human LTBP1-proTGFβ1 complex.

22. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody is an IgG4 or IgG1 subtype.

23. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody is specific for human LTBP1-TGFβ1 complex.

24. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody is specific for human LTBP3-TGFβ1 complex.

25. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody is specific for human LTBP1-TGFβ1 complex and human LTBP3-TGFβ1 complex.

26. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody does not bind a human GARP-TGFβ1 complex or GARP-TGFβ3 complex.

27. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a human LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured by Bio-Layer Interferometry (BLI).

28. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a human LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured by Bio-Layer Interferometry (BLI).

29. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a human LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

30. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a human LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

31. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 27-30, wherein the antibody, or antigen-binding fragment thereof, is cross-reactive with mouse LTBP1-proTGFβ1.

32. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 27-30, wherein the antibody, or antigen-binding fragment thereof, is cross-reactive with mouse LTBP3-proTGFβ1.

33. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 27-30, wherein the antibody, or antigen-binding fragment thereof, is cross-reactive with both mouse LTBP1-proTGFβ1 and mouse LTBP3-proTGFβ1.

34. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 50 nM as measured by Bio-Layer Interferometry (BLI).

35. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 50 nM as measured by Bio-Layer Interferometry (BLI).

36. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

37. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

38. The antibody, or antigen-binding fragment thereof, according to any one of the preceding embodiments, wherein the antibody, or antigen-binding fragment thereof, is isoform-specific in that it selectively binds and inhibits the activation of TGFβ1 associated with LTBP1/3.

39. The antibody, or antigen-binding fragment thereof, according to embodiment 38, wherein the antibody, or antigen-binding fragment thereof, does not bind GARP- TGFβ1.

40. An antibody, or antigen-binding fragment thereof, comprising the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTFRSYVMH (SEQ ID NO: 166);

b) CDR-H2 comprising the amino acid sequence VISHEGS(X_1)KYYADSVKG, wherein: X_1 is L or G (SEQ ID NO: 366); and

c) CDR-H3 comprising the amino acid sequence A(X_1)PRIAARRGGFG(X_2), wherein: X_1 is V, R or L; and X_2 is Y, S or T (SEQ ID NO: 367);

d) CDR-L1 comprising the amino acid sequence TRS(X_1)G(X_2)ID(X_3)NYVQ, wherein, X_1 is S or H; X_2 is N, L, S or A; and X_3 is N, D or Y (SEQ ID NO: 368);

e) CDR-L2 comprising the amino acid sequence ED(X_1)(X_2)RPS, wherein: X_1 is N, F or A; and X_2 is Q, I or V (SEQ ID NO: 369); and

f) CDR-L3 comprising the amino acid sequence Q(X_1)YD(X_2)(X_3)(X_4)Q(X_5)VV, wherein: X_1 is S or G; X_2 is S, F, Y, D, H or W; X_3 is N, D or S; X_4 is N, A, L, E or T; and X_5 is G, R, A or L (SEQ ID NO: 370).

41. The antibody, or antigen-binding fragment thereof, according to embodiment 40, wherein:
within CDR-H3: X_1 is R or L.

42. The antibody, or antigen-binding fragment thereof, according to embodiment 41, wherein:
within CDR-L3: X_2 is Y.

43. The antibody, or antigen-binding fragment thereof, according to embodiment 42, wherein: within CDR-L3: X_3 is D; and X_4 is T.

44. The antibody, or antigen-binding fragment thereof, according to embodiment 42, wherein: within CDR-L3: X_3 is D; X_4 is N; and X_5 is A.

45. The antibody, or antigen-binding fragment thereof, according embodiment 41, wherein: within CDR-L1: X_1 is S or H; X_2 is N or A; and X_3 is N, D or Y; within CDR-L2: X_1 is N or F; and X_2 is Q or V; and within CDR-L3: X_1 is S or G; X_2 is S, Y, D or W; X_3 is D or S; X_4 is N, L or T; and X_5 is G, R, A or L.

46. The antibody, or antigen-binding fragment thereof, according to embodiment 45, wherein: within CDR-L1: X_1 is S; X_2 is N; and X_3 is N or Y; within CDR-L2: X_1 is N; and X_2 is Q or V; and within CDR-L3: X_1 is S or G; X_2 is S, Y or W; X_3 is D; X_4 is N or T; and X_5 is G, R or A.

47. The antibody, or antigen-binding fragment thereof, according to embodiment 46, wherein: within CDR-L3: X_1 is S; X_2 is S or Y; X_3 is D; X_4 is N or T; and X_5 is G, R or A.

48. The antibody, or antigen-binding fragment thereof, according to embodiment 47, wherein: within CDR-L3: X_1 is S; X_2 is Y; X_3 is D; X_4 is N or T; and X_5 is G or A.

49. The antibody, or antigen-binding fragment thereof, according to embodiment 48, wherein: within CDR-L3: X_1 is S; X_2 is Y; X_3 is D; X_4 is T; and X_5 is G.

50. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 45-49, wherein:

a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 166;
b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 167;
c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 168;
d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 169;
e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 170; and
f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 171.

51. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 40-50, which comprises:

a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 318; and

a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 319.

52. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 40-51, which competes or cross-competes with an antibody having a heavy chain variable region sequence as set forth in SEQ ID NO: 318 and light chain variable region sequence as set forth in SEQ ID NO: 319.

53. An antibody, or antigen-binding fragment thereof, which selectively binds to human LTBP1-TGFβ1 complex and human LTBP3-TGFβ1 complex and competes or cross-competes with an antibody having a heavy chain variable region sequence as set forth in SEQ ID NO: 318 and light chain variable region sequence as set forth in SEQ ID NO: 319.

54. An antibody, or antigen-binding fragment thereof, comprising the following six CDRs:

g) CDR-H1 comprising the amino acid sequence G(X_1)I(X_2)S(X_3)SYYW(X_4), wherein, optionally: X_1 is S; X_2 is S, H or R; X_3 is S or G; and, X_4 is G, I, N or V (SEQ ID NO: 386);

h) CDR-H2 comprising the amino acid sequence SISYS(X_1)(X_2)TYY, wherein, optionally: X_1 is G or A; and X_2 is S or T (SEQ ID NO: 398);

i) CDR-H3 comprising the amino acid sequence A(X_1)DPSYDS(X_2)AGM(X_3)V, wherein, optionally: X_1 is R, S or G; X_2 is A or I; and X_3 is D or Q (SEQ ID NO: 387);

j) CDR-L1 comprising the amino acid sequence RAS(X_1)(X_2)IS(X_3)YLN, wherein, optionally: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y (SEQ ID NO: 389);

k) CDR-L2 comprising the amino acid sequence (X_1)AS(X_2)(X_3)QS, wherein, optionally: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R (SEQ ID NO: 390);

l) CDR-L3 comprising the amino acid sequence QQ(X_1)(X_2)D(X_3)P(X_4)T, wherein, optionally: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L (SEQ ID NO: 391).

55. The antibody, or antigen-binding fragment thereof, according to embodiment 54, wherein:

a) within CDR-H1: X_1 is S; X_2 is S or R; X_3 is S; and, X_4 is G;

b) within CDR-H2: X_1 is G or A; and X_2 is S or T;

c) within CDR-H3: X_1 is R, S or G; X_2 is A or I; and X_3 is D or Q;

d) within CDR-L1: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y;

e) within CDR-L2: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R; and

f) within CDR-L3: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L.

56. The antibody, or antigen-binding fragment thereof, according to embodiment 55, wherein:

a) CDR-H1 comprises the amino acid sequence GSIRSSSYYWG (SEQ ID NO: 292);

b) CDR-H2 comprises the amino acid sequence SISYSATTYY (SEQ ID NO: 293);

c) within CDR-H3: X_1 is S or G; X_2 is A or I; and X_3 is D or Q;

d) within CDR-L1: X_1 is K or Q; X_2 is V or S; and X_3 is S or Y;

e) within CDR-L2: X_1 is Y, A or S; X_2 is S or N; and X_3 is L or R; and

f) within CDR-L3: X_1 is S or G; X_2 is F or N; X_3 is W or F; and X_4 is F or L.

57. The antibody, or antigen-binding fragment thereof, according to embodiment 56, wherein:

g) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 292;

h) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 293;

i) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 294;

j) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 295;

k) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 296; and

l) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 297.

58. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 54-57, which is an antibody according to any one of claims 1-5.

59. The antibody, or antigen-binding fragment thereof, according to any one of embodiments 54-58, which comprises:

a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 360; and

a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 361.

selecting affinity matured and/or optimized antibodies, or fragments, that have an IC_{50} of < 50 nM.

182. The method according to embodiments 136-179, wherein the method comprises the step of: selecting affinity matured and/or optimized antibodies, or fragments, that have an IC_{50} of < 25 nM.

183. The method according to embodiments 136-179, wherein the method comprises the step of: selecting affinity matured and/or optimized antibodies, or fragments, that have an IC_{50} of < 10 nM.

184. The method according to embodiments 136-179, wherein the method comprises the step of: selecting affinity matured and/or optimized antibodies, or fragments, that have an IC_{50} of < 5 nM.

185. The method according to any one of embodiments 179-184, wherein the caga assay is an endogenous LTBP caga assay.

186. The method according to any one of embodiments 179-184, wherein the caga assay is a human LTBP overexpression caga assay.

187. The method according to any one of embodiments 179-184, wherein the caga assay is a murine LTBP overexpression caga assay.

188. The antibody or the fragment, use thereof, or related methods thereof, according to any one of the preceding embodiments,

a) which comprises the following variable heavy and/or variable light chain sequences, or a variant thereof:

i) the variable heavy chain sequences QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYVMHWVRQAPGKGLEWVAVISHEGSLKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAVPRIAARRGGFGYWGQGTLVTVSS (SEQ ID NO: 114) or QVQLVESGGGVVQPGRSLRLSCAASGFTFRSYVMHWVRQAPGKGLEWVAVISHEGSLKYY ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPRIAARRGGFGYWGQGTLVTVSS (SEQ ID NO: 318), wherein optionally the variant is at least 85% identical, 90% identical, or 95% identical to the corresponding variable heavy chain sequence.

ii) the variable light chain sequences NFMLTQPHSVSESPGKTVTISCTRSSGNIDNNYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRF SGSIDSSSNSASLTISGLKTEDEADYYCQSYDSDNQGVVFGGGTKLTVL (SEQ ID NO: 89) or NFMLTQPHSVSESPGKTVTISCTRSSGNIDNNYVQWYQQRPGSSPTTVIYEDNQRPSGVPDRF SGSIDSSSNSASLTISGLKTEDEADYYCQSYDSDNQGVVFGGGTKLTVL (SEQ ID NO: 89), wherein optionally the variant is at least 85% identical, 90% identical, or 95% identical to the corresponding variable light chain sequence;

b) which has the following variable heavy chain CDR sequences, or variant thereof:

i) CDR-H1 of FTFRSYVMH (SEQ ID NO: 166) optionally comprising one or more amino acid changes;

ii) CDR-H2 of VISHEGSLKYYADSVKG (SEQ ID NO: 167) optionally comprising one or more amino acid changes; and/or;

iii) CDR-H3 of AVPRIAARRGGFGY (SEQ ID NO: 110) or ARPRIAARRGGFGY (SEQ ID NO: 168) optionally comprising one or more amino acid changes; and/or;

c) which has the following variable light chain CDR sequences, or variant thereof:

i) CDR1-L1 of TRSSGNIDNNYVQ (SEQ ID NO: 169) optionally comprising one or more amino acid changes;

ii) CDR-L2 of EDNQRPS (SEQ ID NO: 170) optionally comprising one or more amino acid changes; and/or;

iii) CDR-L3 of QSYDSDNQGVV (SEQ ID NO: 113) optionally comprising one or more amino acid changes.

A1. An isolated antibody that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ complex;

wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3;

wherein the antibody is a fully human or humanized antibody, or antigen-binding fragment thereof,

wherein the antibody comprises at least three CDRs selected from the following, optionally comprising up to 3 amino acid changes for each of the CDRs:

CDR-H1: SEQ ID NO:100;

CDR-H2: SEQ ID NO:101;

CDR-H3: SEQ ID NO:102;

CDR-L1: SEQ ID NO:103;

CDR-L2: SEQ ID NO:104; and,

CDR-L3: SEQ ID NO:105.

A1.1. An isolated antibody that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ complex;

wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3;

wherein the antibody is a fully human or humanized antibody, or antigen-binding fragment thereof,

wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:100 (SEQ ID NO: 100 comprising these substitutions is disclosed as SEQ ID NO: 400), with the proviso that:

i. the serine residue at position 4 of SEQ ID NO:100 may be substituted with a histidine;

ii. the serine residue at position 7 of SEQ ID NO:100 may be substituted with an alanine or glycine; and/or,

iii. the glycine residue at position 11 of SEQ ID NO:100 may be substituted with a threonine, serine, histidine, leucine, isoleucine, asparagine, valine, or alanine;

b) CDR-H2: SEQ ID NO:101 (SEQ ID NO: 101 comprising these substitutions is disclosed as SEQ ID NO: 401), with the proviso that:

i. the serine residue at position 3 of SEQ ID NO:101 may be substituted with an alanine;

ii. the glycine residue at position 6 of SEQ ID NO:101 may be substituted with an alanine or serine; and/or,

iii. the serine residue at position 7 of SEQ ID NO:101 may be substituted with a threonine;

c) CDR-H3: SEQ ID NO:102, optionally comprising up to three amino acid changes;

d) CDR-L1: SEQ ID NO:103, optionally comprising up to three amino acid changes;

e) CDR-L2: SEQ ID NO:104, optionally comprising up to three amino acid changes; and,

f) CDR-L3: SEQ ID NO:105, optionally comprising up to three amino acid changes.

A2. An isolated antibody that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ complex;

wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3;

wherein the antibody is a fully human or humanized antibody, or antigen-binding fragment thereof;

wherein the antibody comprises a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: SEQ ID NO: 106; and/or,

wherein the antibody comprises a variable light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 107.

A3. The antibody according to embodiment A2, wherein the antibody comprises:

a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 106; and

a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 107.

A3.1 An isolated antibody that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ complex;

wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3;

wherein the antibody is a fully human or humanized antibody, or antigen-binding fragment thereof,

wherein the antibody comprises at least three of the following six CDRs:

a) CDR-H1: SEQ ID NO:94 (SEQ ID NO: 94 comprising these substitutions is disclosed as SEQ ID NO: 399), with the proviso that:
   i. the threonine residue at position 2 of SEQ ID NO:94 may be substituted with an alanine;
   ii. the asparagine residue at position 4 of SEQ ID NO:94 may be substituted with an alanine, tyrosine, aspartate, serine, arginine, or histidine;
   iii. the asparagine residue at position 5 of SEQ ID NO:94 may be substituted with a glutamine, serine, glycine, lysine, glutamate, arginine, or histidine;
   iv. the tyrosine residue at position 6 of SEQ ID NO:94 may be substituted with a arginine;
   v. the proline residue at position 7 of SEQ ID NO:94 may be substituted with a glycine, alanine, leucine, serine, asparagine, valine, aspartate, or glutamine;
   vi. the isoleucine residue at position 8 of SEQ ID NO:94 may be substituted with a methionine or leucine; and/or,
   vii. the histidine residue at position 9 of SEQ ID NO:94 may be substituted with a phenylalanine, tyrosine, asparagine, or serine;
b) CDR-H2: SEQ ID NO:95, optionally comprising up to six amino acid changes;
c) CDR-H3: SEQ ID NO:96, optionally comprising up to three amino acid changes;
d) CDR-L1: SEQ ID NO:97, optionally comprising up to three amino acid changes;
e) CDR-L2: SEQ ID NO:98, optionally comprising up to three amino acid changes; and,
f) CDR-L3: SEQ ID NO:99, optionally comprising up to three amino acid changes.

A3.2. An isolated antibody that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, and does not bind a human GARP-proTGFβ complex;

wherein the antibody does not bind mature TGFβ1, mature TGFβ2 or mature TGFβ3;

wherein the antibody is a fully human or humanized antibody, or antigen-binding fragment thereof;

CLAIMS

What is claimed is:

1. An antibody, or antigen-binding fragment thereof, which specifically binds human LTBP1-TGFβ1 complex and human LTBP3-TGFβ1 complex, comprising the following six CDRs:

a) CDR-H1 comprising the amino acid sequence FTF(X_1)(X_2)YVMH, wherein: X_1 is S or R; and X_2 is G or S;

b) CDR-H2 comprising the amino acid sequence (X_1)ISHEGS(X_2)KYYADSVKG, wherein: X_1 is V or S; X_2 is F or L; and

c) CDR-H3 comprising the amino acid sequence ARPRI(X_1)ARRGGFGY, wherein X_1 is A or L ;

d) CDR-L1 as set forth in SEQ ID NO:97, comprising up to three amino acid changes;

e) CDR-L2 as set forth in SEQ ID NO:98, comprising up to three amino acid changes; and

f) CDR-L3 as set forth in SEQ ID NO:99, comprising up to three amino acid changes.

2. The antibody, or antigen-binding fragment thereof according to claim 1, wherein the antibody comprises:

a heavy chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 88; and

a light chain variable region having an amino acid sequence that is at least 90% identical to SEQ ID NO: 89.

3. The antibody, or antigen-binding fragment thereof, according to claim 1 or 2, wherein the up to three amino acid changes comprises up to two amino acid changes.

4. The antibody, or antigen-binding fragment thereof, according to any one of claims 1-3, wherein:

a) CDR-H1 comprises the amino acid sequence of SEQ ID NO: 166;

b) CDR-H2 comprises the amino acid sequence of SEQ ID NO: 167;

c) CDR-H3 comprises the amino acid sequence of SEQ ID NO: 168;

d) CDR-L1 comprises the amino acid sequence of SEQ ID NO: 169;

e) CDR-L2 comprises the amino acid sequence of SEQ ID NO: 170; and

f) CDR-L3 comprises the amino acid sequence of SEQ ID NO: 171.

5. The antibody, or antigen-binding fragment thereof, of claim 1, which comprises the CDR sequences:

i) CDR-H1 as set forth in SEQ ID NO: 116;

ii) CDR-H2 as set forth in SEQ ID NO: 117; and;

iii) CDR-H3 as set forth in SEQ ID NO: 118.

6. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which has a variable heavy chain sequence as set forth in SEQ ID NO: 122.

7. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which binds a human LTBP1-proTGFβ1 complex and a human LTBP3-TGFβ1 complex with a K_D of < 5 nM as measured by Bio-Layer Interferometry (BLI), optionally < 1nM.

31. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which is cross-reactive with mouse LTBP1-proTGFβ1.

8. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, which is cross-reactive with mouse LTBP3-proTGFβ1.

9. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP1-proTGFβ1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

10. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or antigen-binding fragment thereof, binds a mouse LTBP3-proTGFβ1 complex with a K_D of < 10 nM as measured by Bio-Layer Interferometry (BLI).

11. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody, or antigen-binding fragment thereof cross-reacts with human and murine LTBP1-proTGFβ1 and LTBP3-proTGFβ1 complexes, each with a KD of < 5 nM or optionally < 1 nM.

12. The antibody, or antigen-binding fragment thereof, according to any one of the preceding claims, wherein the antibody is an IgG4 or IgG1 subtype, optionally wherein the antibody is a human IgG4 subtype and comprises a backbone substitution of Ser to Pro that produces an IgG1-like hinge.

13. The antibody, or antigen-binding fragment thereof, according to any one of the proceeding claims, wherein the antibody, or the antigen-binding fragment thereof comprises a mutation in a constant region.

14. A pharmaceutical composition comprising the antibody of any one of the preceding claims and a pharmaceutically acceptable excipient.

15. The pharmaceutical composition according to claim 14, which is prepared for intravenous administration or subcutaneous administration.

16. A composition comprising a multi-dose vial containing the pharmaceutical composition of claim 14 or 15.

17. A composition comprising a single-dose syringe containing the pharmaceutical composition of claim 14 or 15, optionally wherein the syringe is a disposable syringe.

18. Use of the composition of any one of claims 14-17 in the manufacture of a medicament for treating a fibrotic disorder in a human subject.

19. The use according to claim 18, wherein the fibrotic disorder is an organ fibrosis.

20. The use according to claim 19, wherein the organ fibrosis is an advanced organ fibrosis.

21. The use according to claim 19 or 20, wherein the organ fibrosis is selected from the group consisting of: kidney fibrosis, liver fibrosis, lung fibrosis, cardiac fibrosis, pancreatic fibrosis, skin fibrosis, scleroderma, muscle fibrosis, uterine fibrosis and endometriosis.

22. The use according to claim 21, wherein the lung fibrosis is idiopathic pulmonary fibrosis (IPF).

23. The use according to claim 21, wherein the subject has chronic kidney disease (CKD).

24. The use according to claim 21, wherein the liver fibrosis is associated with nonalcoholic steatohepatitis (NASH).

25. The use according to any one of claims 18-24, wherein the medicament is to be administered to the subject at a dosage of between 0.1 and 30 mg/kg.

26. The use according to claim 25, wherein the medicament is to be administered twice a week, once a week, once every 2 weeks, once every 3 weeks, once a month, or every other month.

27. The use according to claim 25, wherein a therapeutic regimen comprises an initial phase of a therapy and a subsequent phase of the therapy, wherein the subject receives a loading dose during the initial phase followed by a maintenance dose during the subsequent phase.

28. The use according to claim 27, wherein the loading dose is between 2-30 mg/kg, and the maintenance dose is between 0.1-20 mg/kg.

29. The use according to claim 27 or 28, wherein the loading dose is to be administered to the subject twice a week or once a week.

30. The use according to any one of claims 27-29, wherein the maintenance dose is to be administered to the subject once every 2-8 weeks.

31. The use according to any one of claims 18-30, wherein the use further comprises testing or confirming expression of TGFβ1, LTBP1 or LTBP3 in a biological sample collected from the subject.

32. A method for making a composition of any one of claims 14-17, comprising an antibody, or antigen-binding fragment thereof, that specifically binds a human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex, , wherein the antibody, or the antigen-biding fragment thereof, does not show detectable binding to a human GARP-proTGFβ1 or human LRRC33-proTGFβ1 complex, the method comprising steps of:

i) selecting an antibody or an antigen-binding fragment thereof that dissociates from human LTBP1-proTGFβ complex and/or a human LTBP3-proTGFβ complex with t½ of at least 45 minutes, and,

ii) formulating the antibody or fragment into a pharmaceutical composition,

thereby making the composition comprising the antibody or antigen-binding fragment.

33. The method of claim 32, further comprising the step of: selecting an antibody or antigen-binding fragment with IC50 of < 5 nM as measured by cell-based assays, optionally < 2 nM.

34. The method of claim 32 or 33, further comprising the step of: confirming efficacy in an in vivo preclinical model, wherein optionally the preclinical model is a liver fibrosis model, kidney fibrosis model, or cardiac fibrosis model.

35. The method of any one of claims 32-34, wherein the method further comprises a step of: selecting antibodies or fragments that are cross-reactive to human and rodent antigens.

36. The method of any one of claims 32-35, wherein the method further comprises a step of: subjecting the antibody or fragment that is present in the first pool of antibodies and the second pool of antibodies to affinity maturation and/or optimization, so as to provide an affinity matured and/or optimized antibody or fragment.

37. The composition of any one of claims 14-17 for use in therapy.