Selective Latent TGFβ1 Inhibitors Exhibits Improved Nonclinical Safety Profile

Poster #P533

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Abstract

Perturbation of the TGFβ signaling pathway has been implicated in the pathogenesis of many diseases, including connective tissue disorders, fibrosis, and cancer. Nonselective inhibition of all three TGFβ isoforms (i.e., a pan-TGFβ inhibition approach) is associated with safety liabilities. We have previously shown that a selective latent TGFβ1 inhibitor (SRK-181) has an improved safety profile compared to pan-TGFβ inhibition and is associated with immune cell engagement[1]. While this profile is advantageous for therapeutics in immuno-oncology, it may not be favorable for addressing chronic diseases such as fibrosis. Here, we hypothesize that selective targeting of extracellular matrix-associated TGFβ1 would avoid effects on the immune system, allowing for chronic anti-fibrotic therapy. To that end, we have developed a context-selective antibody, LTBP-49247, that selectively inhibits TGFβ1 large latent complexes, only in the context of LTBP1 and LTBP3 and does not bind to TGFβ1 presented by immune cells via GARP or LRRC33. We have also developed a context-independent TGFβ1-37000 antibody. In contrast to LTBP-49247, TGFβ1-37000 is selective for the TGFβ1 isoform across all large latent complexes. We evaluated the toxicity profile of these selective antibodies in the chronic setting in animal models.

Our data suggest that selective inhibition of latent TGFβ1 provides an improved preclinical safety profile relative to pan-TGFβ inhibition. Further, we have developed molecules with different selectivity profiles for TGFβ large latent complexes which allow for the option of immune cell engagement, as might be desirable in an oncology setting, or immune avoidance which may be promising for chronic diseases such as fibrosis.

Introduction

- TGFβ inhibition is a promising therapeutic intervention for diseases like fibrosis and cancer. Nonselective-TGFβ inhibition of all isoforms is associated with safety liabilities[1,2,3,4,5]
- Scholar Rock has generated a suite of antibodies that are capable of selective TGFβ1 inhibition within different cellular and tissue microenvironments in order to minimize safety effects while retaining antifibrotic efficacy
- Our previously identified context independent, isoform selective TGFβ1 inhibitor was shown to have an improved safety profile compared to non-selective TGFβ inhibition, was associated with on-target immune cell activation, and is advancing in the clinic in immuno-oncology where immune cell activation is desirable
- Scholar Rock has identified LTBP-49247, a highly selective antagonist of matrix-associated LTBP-TGFβ1, and is developing it for the treatment of rare fibrotic disease
- Our safety data suggest that LTBP-49247 may offer a safety profile better suited to treating chronic fibrotic indications in which immune cell activation is undesirable

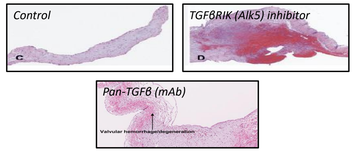
Disclaimer

Any information and recommendations provided by Scholar Rock during this presentation are proprietary to Scholar Rock.

Note: LTBP-49247 is a pre-clinical antibody and has not been approved by the U.S. Food and Drug Administration (FDA), the European Commission, or any other health authority for any indication, and the safety and effectiveness of this molecule have not been established.

Toxicity Has Historically Been a Critical Limitation for Nonselective/Pan-TGFβ Inhibition[2,3,4,5]

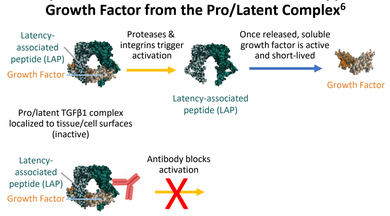
- Cardiac toxicities
  - Valvulopathy (ALK5i and mAb)
  - Marked inflammation, necrosis, degeneration and hyperplasia
- Oral toxicities
  - Dental dysplasia
  - Gingivitis
  - Bleeding
  - Tongue lesions
  - Esophageal lesions
- Mortality



Our Hypothesis: Greater Selectivity May Achieve Superior Safety Profile While Maintaining Efficacy

- Rather than blocking all 3 isoforms (TGFβ1/2/3), can we selectively inhibit one specific isoform?
- By targeting the *pro/latent TGFβ complex*, can we achieve this isoform selectivity?
  - TGFβ1/2/3 growth factors are highly conserved (71-80% identical)
  - TGFβ prodomains are poorly conserved (37-49% identical)
- Advantages may include:
  - Improved safety profile
  - Durability of effects (target is present at rest, prior to activation)
  - Localized effects (tissue/cell-tethered target)

TGFβ1 Activation Involves Release of the "Trapped" Growth Factor from the Pro/Latent Complex[6]



First Latent TGFβ1 Structure, Laboratory of Prof. Timothy Springer; Shi et al. *Nature*. 2011.

Selective Context-Independent TGFβ1 Inhibition Exhibits Better Safety Profile Compared to Pan-TGFβ Inhibition

Context-independent TGFβ Selective Inhibition (SRK-181)

- Cardiac toxicities
  - No valvulopathy
  - No marked inflammation, necrosis, degeneration and hyperplasia
- Oral toxicities
  - No dental dysplasia or gingivitis
  - No bleeding or tongue lesions
  - No esophageal lesions
- 4-week GLP toxicology studies[1]:
  - Rats: NOAEL was 200 mg/kg QW, highest dose tested
  - Cynomolgus monkeys: NOAEL was 300 mg/kg QW, highest dose tested
- No SRK-181 related mortality

Pan-TGFβ Inhibition

- Cardiac toxicities
  - Valvulopathy
  - Marked inflammation, necrosis, degeneration and hyperplasia
- Oral toxicities
  - Dental dysplasia, gingivitis
  - Bleeding
  - Tongue lesions
  - Esophageal lesions
- Mortality

TGFβ1 Isoform Specificity Drives Improved Preclinical Toxicity Profile and is Associated with Immune Cell Activation

Repeat dose pilot toxicology study in adult female Sprague Dawley rats:

Microscopic observations in heart	Control Vehicle iv, qwk x 4	LY2109761 300 mg/kg po, qd x 8	PanTGFβAb 30 mg/kg iv, 1 dose	SRK-181 10 mg/kg iv, qwk x 4	SRK-181 30 mg/kg iv, qwk x 4	SRK-181 100 mg/kg iv, qwk x 4
Valvulopathy						
Atrium—Mixed cell infiltrate						
Myocardium—Degeneration/necrosis						
Myocardium—Hemorrhage						
Myocardium—Mixed cell infiltrate, base						
Coronary artery—Necrosis with inflammation						
Cardiomyocyte—Necrosis/inflammatory cell infiltrate						

LEGEND: Unremarkable; Minimal; Slight; Moderate

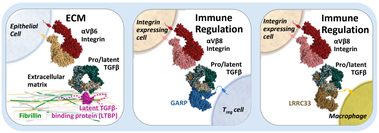
- Cardiac findings were exhibited in animals dosed for 1-week with a pan-TGFβ antibody or ALK5 small molecule (LY2109761) as expected[3,4]
- No cardiotoxicities (valvulopathy) were noted with a TGFβ1 selective antibody: NOAEL (No Observed Adverse Effect Level) was the highest dose evaluated of 100 mg/kg QW[3]
- **This antibody is associated with on-target immune cell activation[7] and is in clinical development for immuno-oncology (IO) to overcome primary resistance to checkpoint therapy**

Can We Retain TGFβ1 Selectivity and Dial Out Immune Cell Activation for a Potential Anti-Fibrotic Therapeutic?

More Exquisite Selectivity Can Be Achieved With Our Approach

- **Context-selective** inhibition of TGFβ1 activation

Latent TGFβ1 Forms Covalent, Large Latent Complexes With a Presenting Molecule[6]



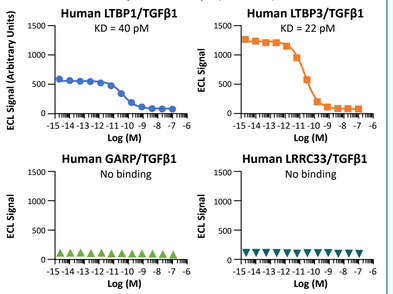
LTBP1 and LTBP3 present TGFβ1 in the ECM. ECM-bound TGFβ1 is relevant to fibrotic tissues

GARP presents TGFβ1 on Tregs necessary to modulate the T cell niche

LRRC33 presents TGFβ1 on myeloid cells

LTBP-49247 Selectively Binds to Human LTBP1/3-TGFβ1 Complexes[6]

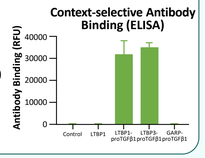
Equilibrium titration to determine affinity to Human Large Latent Complexes of TGFβ1 (MSD-SET)



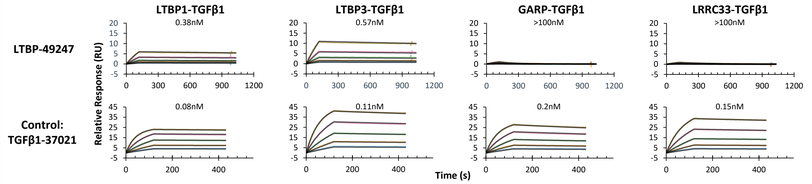
- LTBP1-proTGFβ1
- LTBP3-proTGFβ1
- GARP-proTGFβ1
- LRRC33-proTGFβ1

Components of the *extracellular matrix* (ECM)

Anchored to *immune cell surface*



LTBP-49247 Selectively Binds to LTBP1- and LTBP3-complexed TGFβ1[6]



- LTBP-49247 exhibits high affinity to LTBP1/3-TGFβ1, and >100x selectivity vs. GARP- and LRRC33-TGFβ1
- A control context-independent antibody TGFβ1-37021 exhibits high affinity to LTBP-, GARP-, and LRCC33-TGFβ1
- Both antibodies potently inhibit LTBP-TGFβ1 activation in vitro

Non-GLP 13-Week Toxicology and Toxicokinetic Study in Mice with IP Administration of LTBP-49247 (hIgG4)[6]

Study Design

Group	Treatment	Dose mg/kg/dose	Number of Animals in Tox Groups: Males	Number of Animals in Tox Groups: Females	Number of Animals in TK Groups: Males	Number of Animals in TK Groups: Females
1	Vehicle	0	16	16	3	3
2	49247	10	16	16	24	24
3	49247	30	16	16	24	24
4	49247	100	16	16	24	24

Endpoints:

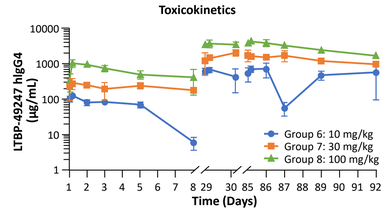
- Mortality, post-dose observations; clinical observations, body weights, food consumption, ophthalmic exams, and hematology, coagulation, clinical chemistry, urinalysis, organ weights, histopathology w/peer review (and detailed heart sectioning)

Notes:

- CD1 mice*
- 3x week LTBP-49247 IP-dosing
- 13-weeks of dosing; 39 total doses
- Separate TK/ADA groups with 24/group/sex

*CD1 mice treated with pan-TGFβ antibody demonstrated toxicity phenotypes.
*More tox historical data available for CD1 mice.

Toxicokinetics Indicate Relevant Dose Exposure



- LTBP-49247 concentrations remained elevated through Day 29 and the final dose on Day 85
- In general, the exposure of LTBP-49247 increased following multiple doses, as assessed by comparing the accumulation ratio of the C_{max} and AUC(0-7).
  - Overall magnitude of accumulation was less than dose proportional
- Following the first dose, the half life ranged from 7.8–11.9 days

Note: In the 10 mg/kg group, the sharp decrease in exposure seen at Day 8 is consistent with target-mediated drug disposition (TMDD).

No Adverse Effect of LTBP-49247 on General Toxicology Parameters

- **No test-article effect on mortality and overall body weight**

Clinical Chemistry:

- **100 mg/kg:** TA-related mild increases (1.25x) in globulin concentration with concomitant decreases in mean albumin/globulin ratio (0.79x); possibly related to IgG from test article and microscopic peritoneal inflammation. Two males had increased urea nitrogen that was of uncertain relationship to the TA
- **30 mg/kg:** one male had changes consistent with a decreased glomerular filtration rate; however, this was of uncertain relationship to the TA. No microscopic correlates in the kidney were observed at the higher dose.

Hematology and Coagulation:

- No test article-related effects on hematology or coagulation parameters in either sex at any dose level

Urinalysis:

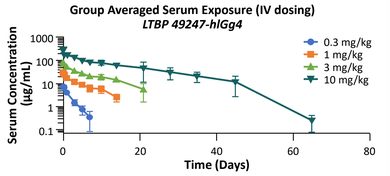
- No test article-related effects on urinalysis parameters in either sex at any dose level

Non-GLP 13-Week Mouse Toxicology Study (LTBP-49247); Key Histopathology Findings Not Relevant to Humans

Peer Reviewed

- No cardiac or oral toxicity findings observed
- No LTBP-49247 treatment related changes in organ weights
  - Increased thymus weights in animals administered ≥10 mg/kg/dose were of uncertain relationship to the test article
- Microscopic findings related to TA administration were limited to Harderian gland *(organ only found in rodents and not relevant to humans)*
- Findings of neutrophilic, mixed cell, or mononuclear cell infiltrates in the mesentery associated with the spleen, pancreas and vaginal tunic was suggestive of an increased inflammatory response to intraperitoneal injection of the antibody test article compared with the vehicle

LTBP-49247 Exhibits Favorable PK in Cynomolgus Monkeys



- LTBP-49247-hIgG4 achieves dose-proportional exposure across each dose
- Target mediated drug disposition (TMDD) observed at ≤10–30 µg/mL exposure,
  - Resulted in increased clearance at exposures at or below this level
  - Consistent with presence of abundant target seen with prior anti-TGFβ1 antibody approaches[1]
- Half-life at doses above the TMDD threshold (≥1mg/kg) range from 4.65–8.11 days

Predicted Human Half-life ~24 Days

Conclusions

Matrix targeted TGFβ inhibition may be preferable to address multiple potential chronic indications

- Context selective inhibition of TGFβ1 demonstrates antifibrotic efficacy in multiple rodent models of fibrosis
- LTBP-49247 is a highly potent, selective antibody with a promising developability profile
- Mouse TK data show that exposure of LTBP-49247 increased following multiple doses. Overall magnitude of accumulation was less than dose proportional
- Cynomolgus monkey PK study predicts ~24-day half-life of LTBP-49247 in humans
- In a preclinical safety study, selective inhibition of matrix targeted LTBP-TGFβ1 avoids known class effect safety liabilities associated with pan-TGFβ inhibition without the risk of immune cell activation

References

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