Discovery and Antifibrotic Activity of an Anti-LTBP-TGFβ1 Inhibitory Antibody

Poster #77

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Apitegromab and SRK-181 are investigational drug candidates under evaluation. Apitegromab and SRK-181 have not been approved for any use by the FDA or any other regulatory agency and the safety and efficacy of apitegromab and SRK-181 have not been established.

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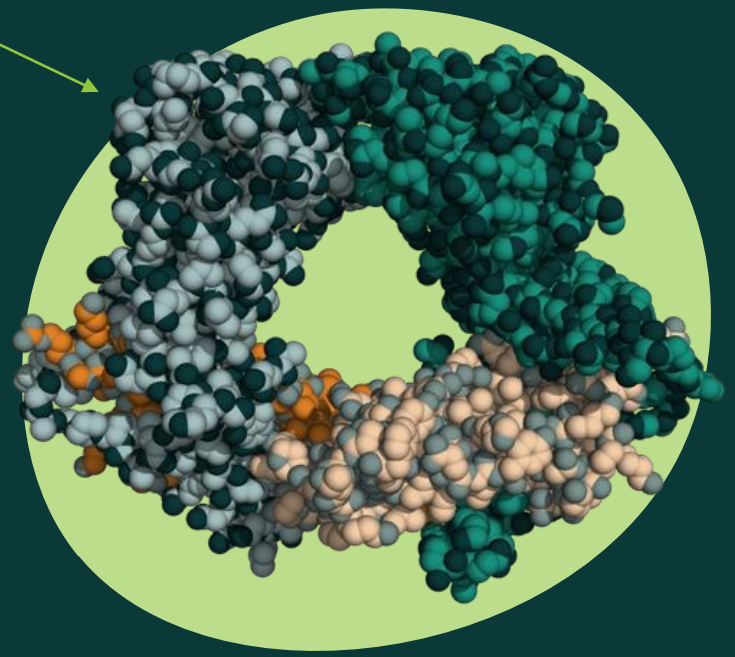
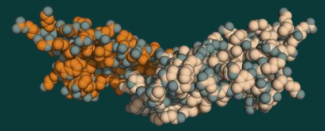
Revolutionary Approach to Regulating TGFβ Superfamily Implicated in Devastating Diseases

Scholar Rock's Target
Latent Growth Factor



Traditional Target
"mature" growth factor



TGFβ Superfamily: Highly Sought-After Targets

Recognized by the industry as important targets given their fundamental roles in regulating a variety of cellular processes

Dysregulation plays a role in devastating diseases that have a high unmet need, including:

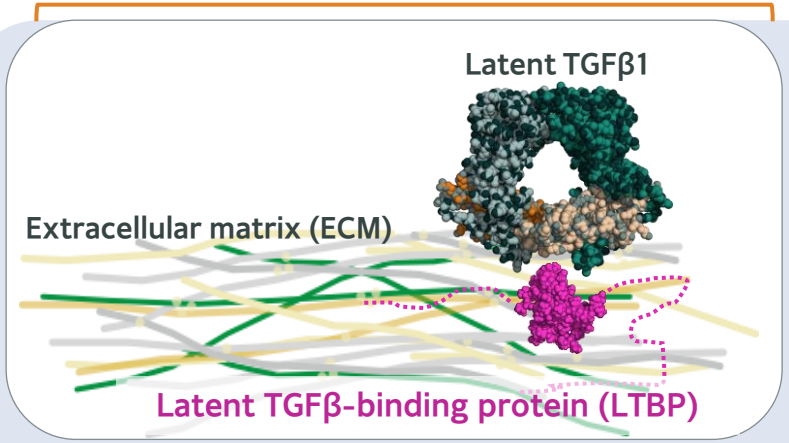
- Neuromuscular disorders
- Fibrosis
- Oncology

Scholar Rock's R&D Platform
Transforming Medical Practice

- Selectively target the latent form of growth factors in the microenvironment of cells and tissues with uniquely designed antibodies
- Overcome the challenges that plague traditional approaches that target the "mature" growth factor, which are difficult to differentiate and lead to unintended negative effects

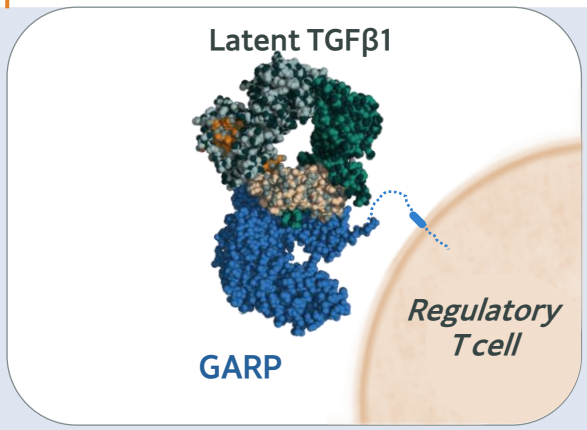
Latent TGFβ1 Forms Covalent, Large Latent Complexes with a Presenting Molecule

Matrix-associated TGFβ1

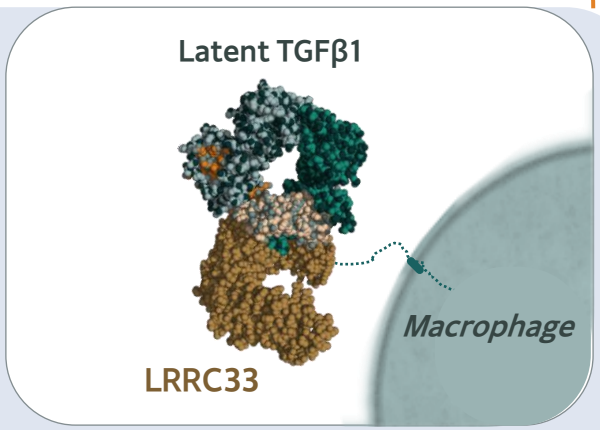


LTBP1 and LTBP3 present TGFβ1 in the ECM

Non-matrix, Immune-associated TGFβ1



GARP presents TGFβ1 on Tregs and endothelial cells



LRRC33 presents TGFβ1 on myeloid cells

Hypothesis: LTBP-TGFβ1 drives fibrotic pathogenesis

Inhibition of immune-associated TGFβ1 results in immune cell activation and inflammation, which could be deleterious in an antifibrotic therapeutic

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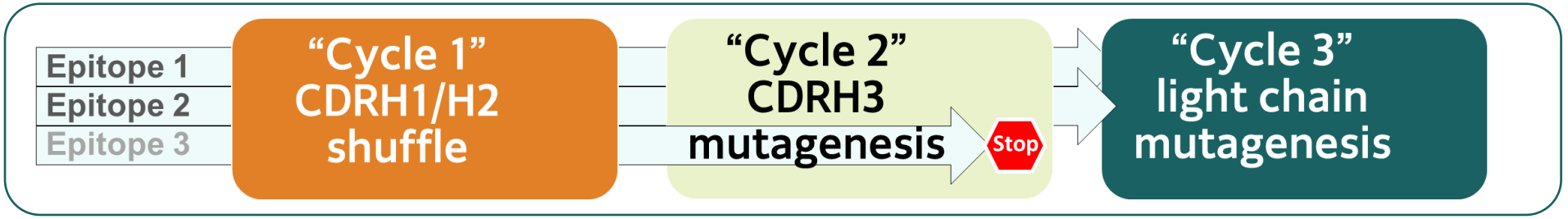
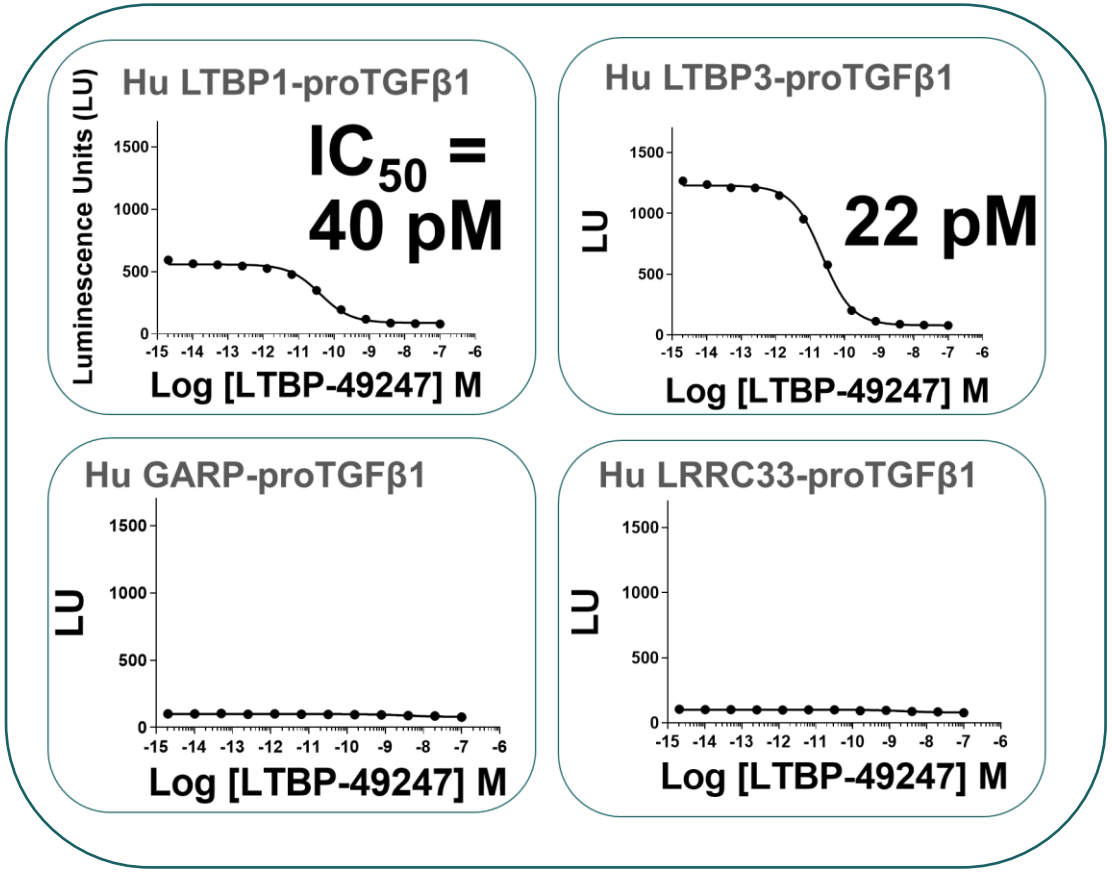
Multiple Rounds of Affinity Maturation were Required to Attain Highly LTBP-TGFβ1 Selective Antibodies





- **Poster #77** describes the affinity maturation campaign deployed to engineer **LTBP-49247**, a pM affinity antibody specific to LTBP complexes of TGFβ1
- Binding measured by a Meso Scale Discovery solution equilibrium titration assay
- LTBP-49247 is cross-reactive to mouse, rat, and cyno LTBP-TGFβ1

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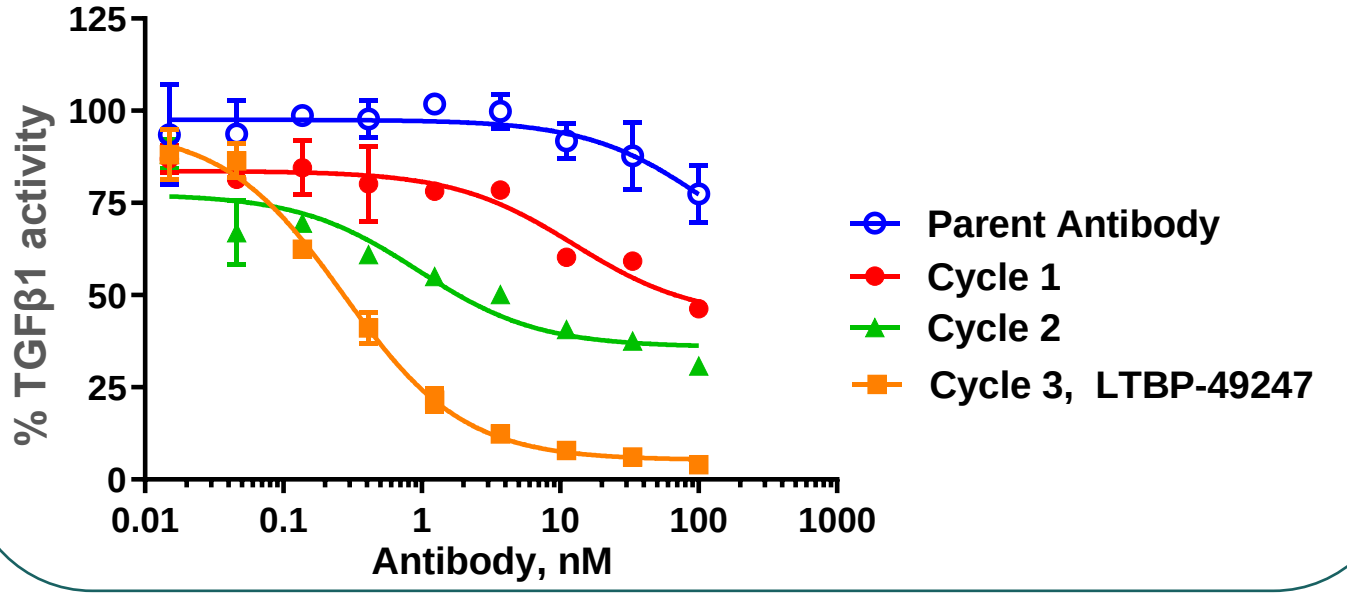
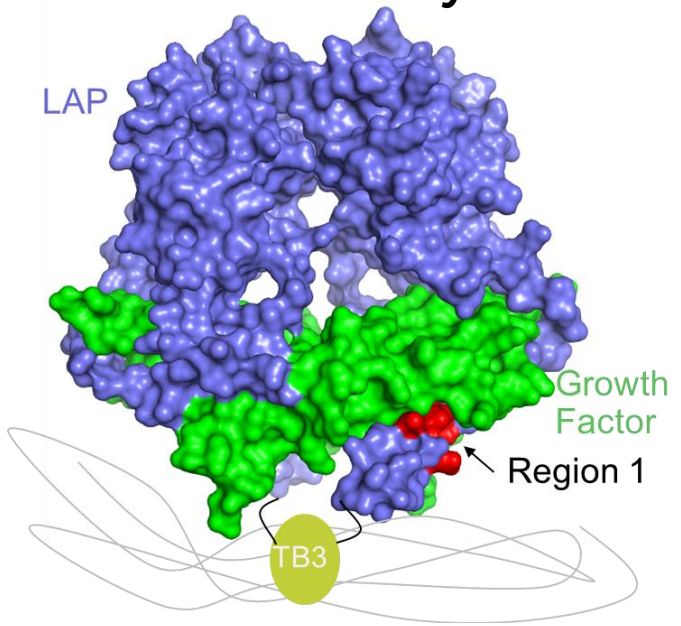
HDX Informs the Mechanism of LTBP-TGFβ1 Selectivity as Well as The Mechanism of Inhibitory Activity

LTBP-49247 potently inhibits integrin-mediated activation of LTBP-TGFβ1



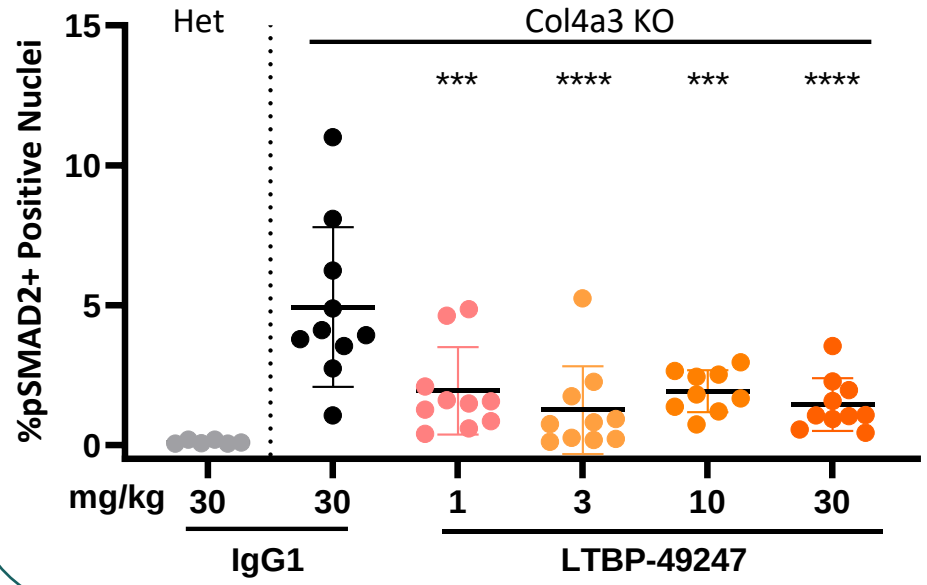
Region 1 is most protected by LTBP-49247 by HDX



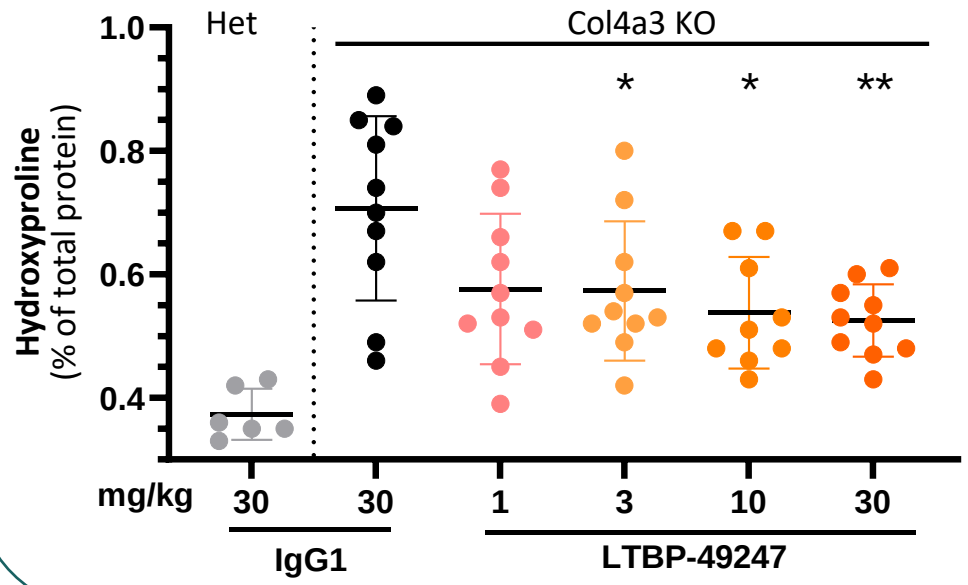
- Structural studies elucidate the epitope of LTBP-49247 on the small latent complex of TGFβ1
  - Epitope is very close to the presenting molecule, predicted clash with GARP & LRRC33
  - Binding to both latency associated peptide (LAP) and growth factor

LTBP-49247 Reduces pSmad2 and Fibrosis in a Mouse Model of Alport Syndrome

TGFβ Signaling (pSMAD2)



Fibrosis (Collagen Content)



- Alport Syndrome is a rare genetic disease caused by mutations in COL4
  - Disease is characterized by progressive kidney injury and fibrosis
- Model above is in Col4A3$^{-/-}$ mice
- Potent effect with LTBP-49247 down to 1 mg/kg dose

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Summary

- Scholar Rock's approach of targeting latent growth factors has enabled unprecedented specificity in targeting the TGFβ superfamily

- Extensive affinity maturation deployed to engineer LTBP-49247, an antibody that inhibits the activation of LTBP-TGFβ1

- **Selective inhibition of matrix-associated LTBP-TGFβ1 exhibits target engagement and anti-fibrotic efficacy in a preclinical rodent model of kidney fibrosis (Alport)**
  - **Avoids safety liabilities associated with pan-TGFβ inhibition**
  - **Does not trigger immune cell activation associated with targeting TGFβ1 in the immune milieu**

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Thank you!

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