STRUCTURAL CHARACTERIZATION OF SELECTIVE INHIBITORS OF TGFβ1 ACTIVATION WITH DIFFERING MECHANISMS OF ACTION AND CLINICAL POTENTIAL

Monday July 22, 2024

F. Chuck Streich Jr.

Principal Scientist

Scholar Rock Inc.

Cambridge, MA

Forward-Looking Statements

Various statements in this presentation concerning the future expectations, plans and prospects of Scholar Rock, Inc. (“Scholar Rock”), including without limitation, Scholar Rock’s expectations regarding its strategy, its product candidate selection and development timing, including timing for the initiation of and reporting results from its preclinical studies and clinical trials for SRK-439, apitegromab, SRK-181, and other product candidates and indication selection and development timing, its cash runway, the ability of any product candidate to perform in humans in a manner consistent with earlier nonclinical, preclinical or clinical trial data, and the potential of its product candidates and proprietary platform. The use of words such as “may,” “could,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify such forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. All such forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, without limitation, that preclinical and clinical data, including the results from the Phase 2 trial of apitegromab or Part A or Part B of the Phase 1 trial of SRK-181, are not predictive of, may be inconsistent with, or more favorable than, data generated from future or ongoing clinical trials of the same product candidate, including the Phase 3 clinical trial of apitegromab in SMA and Part B of the Phase 1 clinical trial of SRK-181, respectively, Scholar Rock’s ability to provide the financial support, resources and expertise necessary to identify and develop product candidates on the expected timeline, the data generated from Scholar Rock’s nonclinical and preclinical studies and clinical trials, information provided or decisions made by regulatory authorities, competition from third parties that are developing products for similar uses, Scholar Rock’s ability to obtain, maintain and protect its intellectual property, the success of Scholar Rock’s current and potential future collaborations, Scholar Rock’s dependence on third parties for development and manufacture of product candidates including, without limitation, to supply any clinical trials, Scholar Rock’s ability to manage expenses and to obtain additional funding when needed to support its business activities and establish and maintain strategic business alliances and new business initiatives, and the impacts of current macroeconomic and geopolitical events, hostilities in Ukraine, increasing rates of inflation and rising interest rates, on business operations and expectations, as well as those risks more fully discussed in the section entitled "Risk Factors" in Scholar Rock’s Form 10-K for the year ended December 31, 2022, and Quarterly Report on Form 10-Q for the quarter ended September 30, 2023, as well as discussions of potential risks, uncertainties, and other important factors in Scholar Rock’s subsequent filings with the Securities and Exchange Commission. Any forward-looking statements represent Scholar Rock’s views only as of today and should not be relied upon as representing its views as of any subsequent date. All information in this press release is as of the date of the release, and Scholar Rock undertakes no duty to update this information unless required by law.

This presentation may also contain estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we compete are necessarily subject to a high degree of uncertainty and risk.

Apitegromab and SRK-181 are investigational drug candidates under evaluation. Apitegromab, SRK-181, and SRK-439 have not been approved for any use by the FDA or any other regulatory agency and the safety and efficacy of apitegromab, SRK-181 and SRK-439 have not been established.

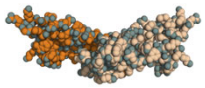
ScholarRock™

Our Approach

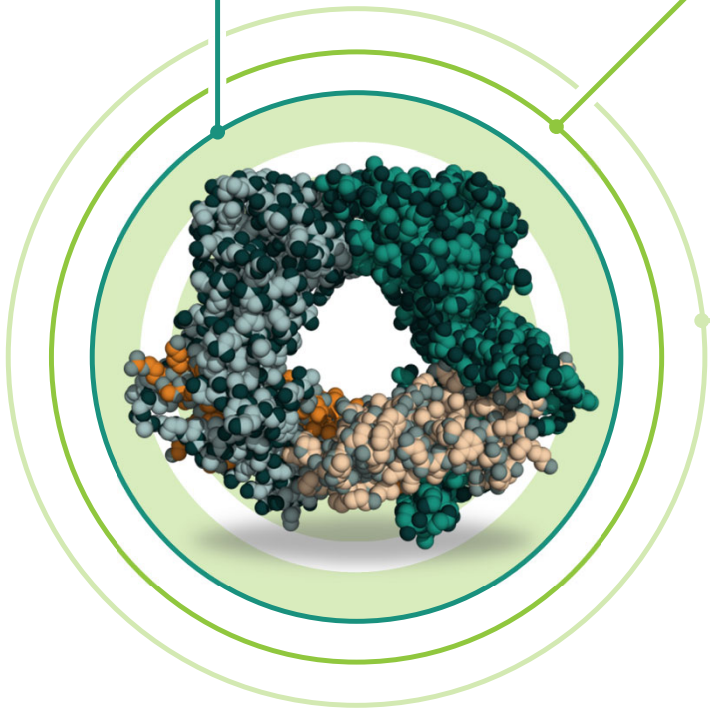
Selectivity Drives Success

RIGHT TARGET → **Validated Biology**

RIGHT TIME → **Latent Form**



Traditional Target
"mature" active growth factor



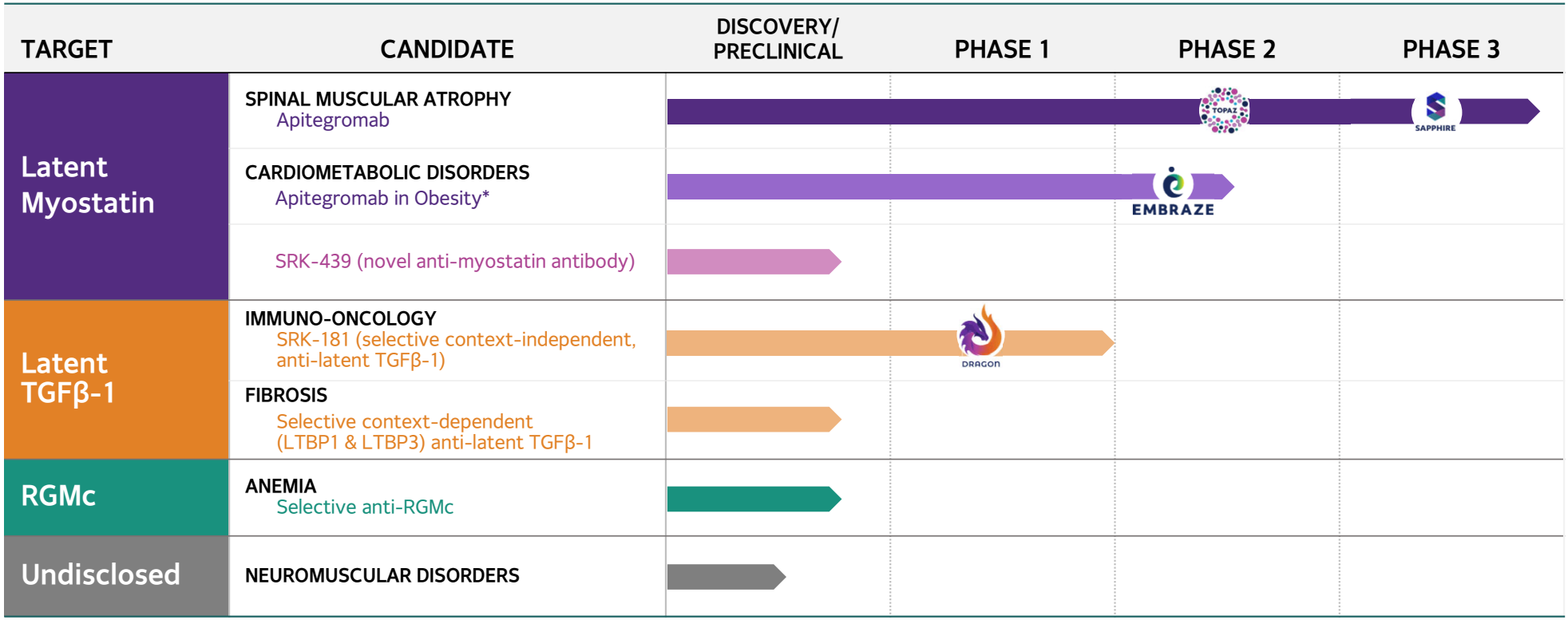
Scholar Rock's Target
Latent Growth Factor

Deep structural insights to validated targets

Industry-leading antibody design and protein engineering to selectively target latent growth factors

Optimized for efficacy and mitigates off-target effects

Growing Pipeline Across High Value Therapeutic Areas



*Utilized data from previously completed Ph 1 study in healthy volunteers and initiate a Ph 2 POC trial in 2024.
LTBP1=Latent transforming growth factor beta binding protein 1; LTBP3=Latent transforming growth factor beta binding protein 3; POC=Proof of concept; RGMc=Repulsive guidance molecule C; TGFβ-1=Transforming growth factor beta-1.

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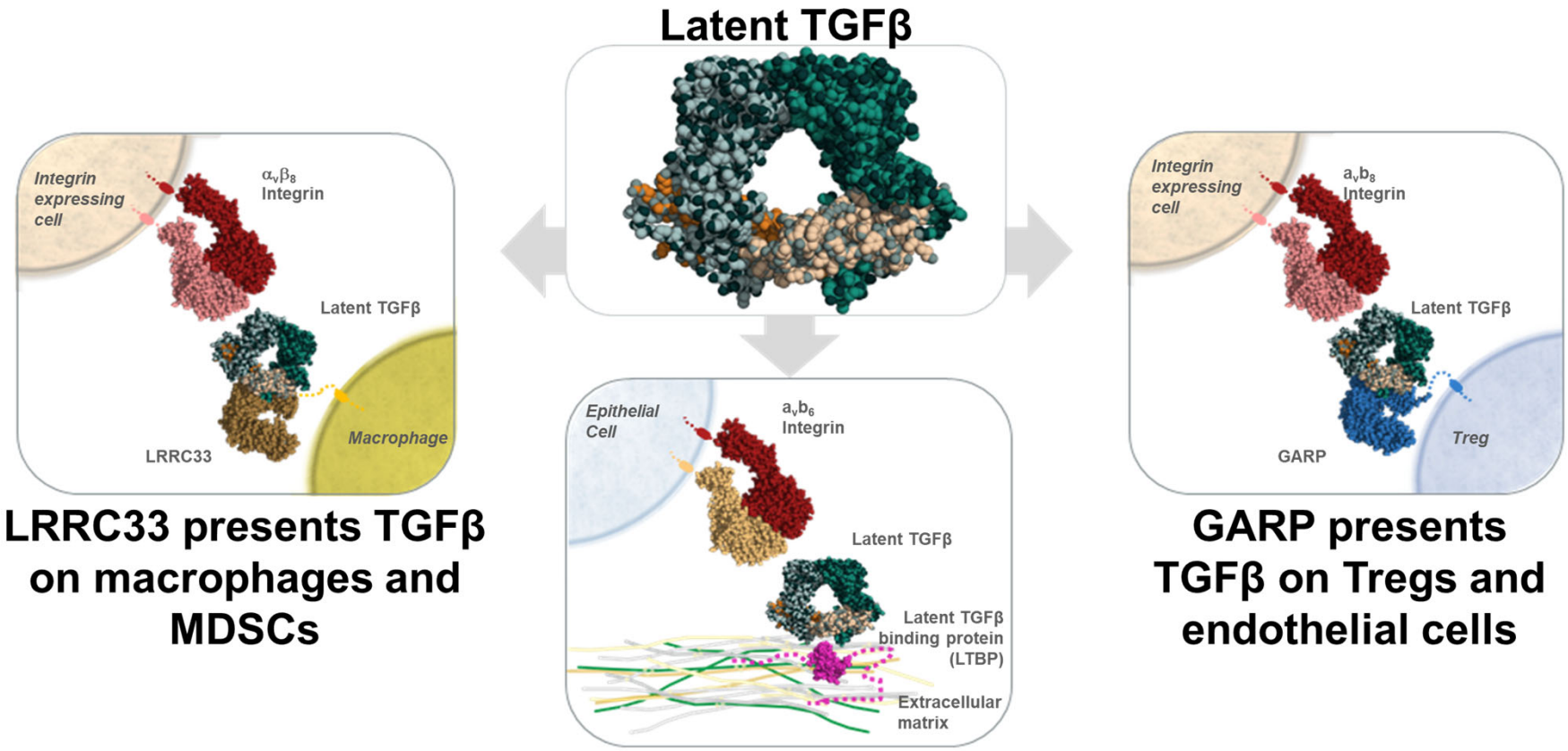
TGFβ1 is a potent signaling molecule, poised for activation within different contexts



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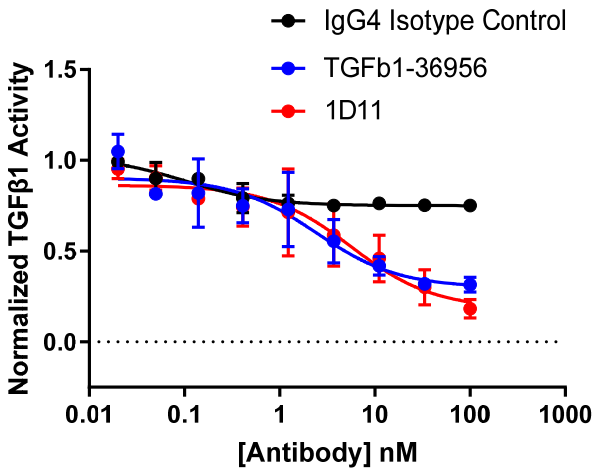
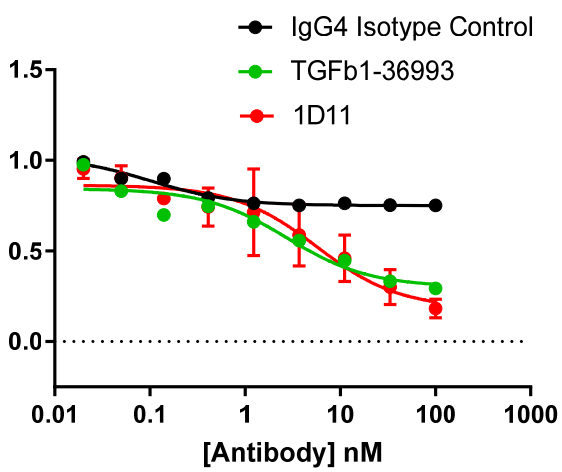
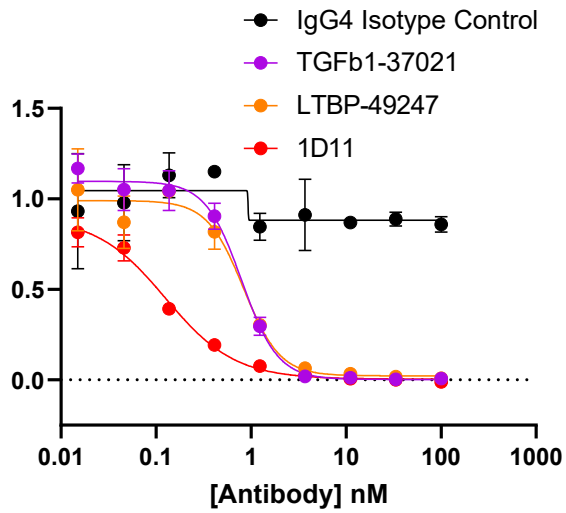
Scholar Rock has discovered several antibody inhibitors of integrin-mediated activation of latent TGFβ1







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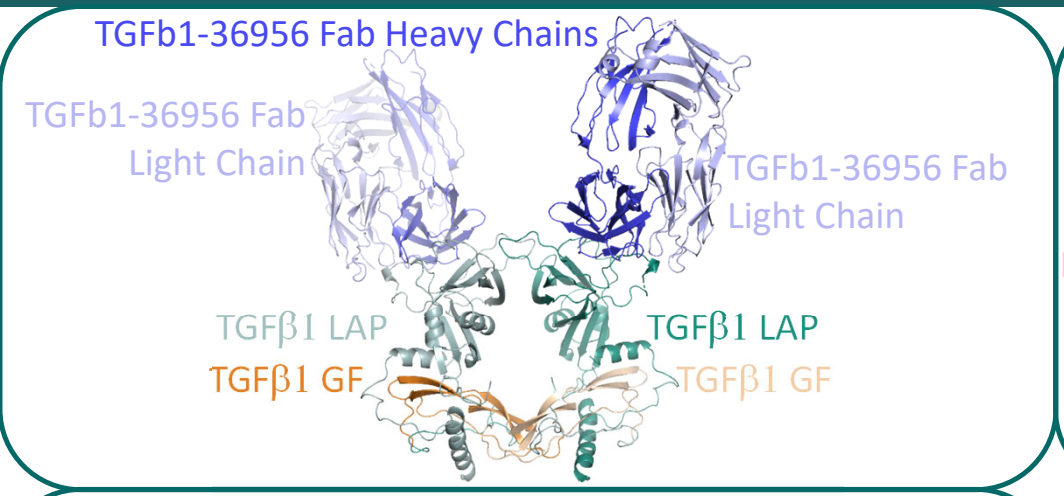
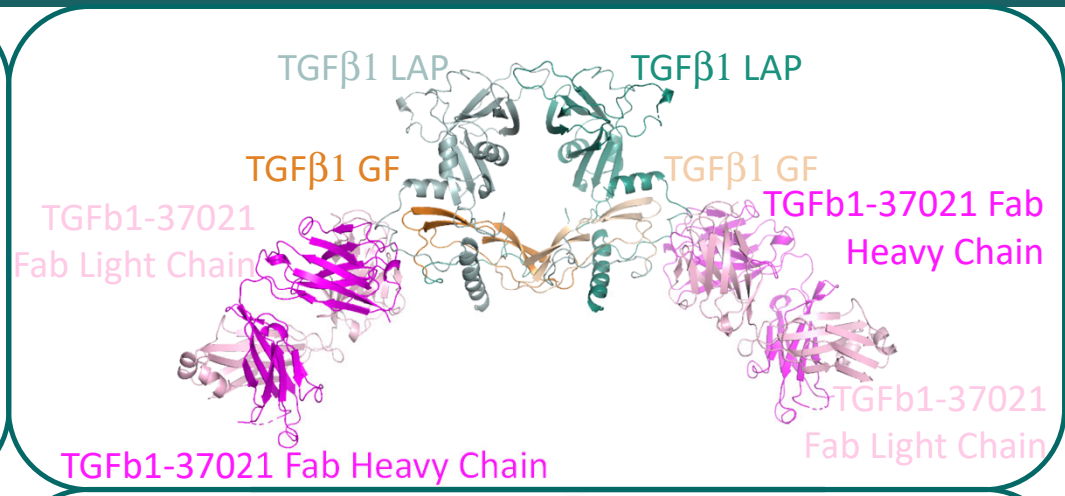
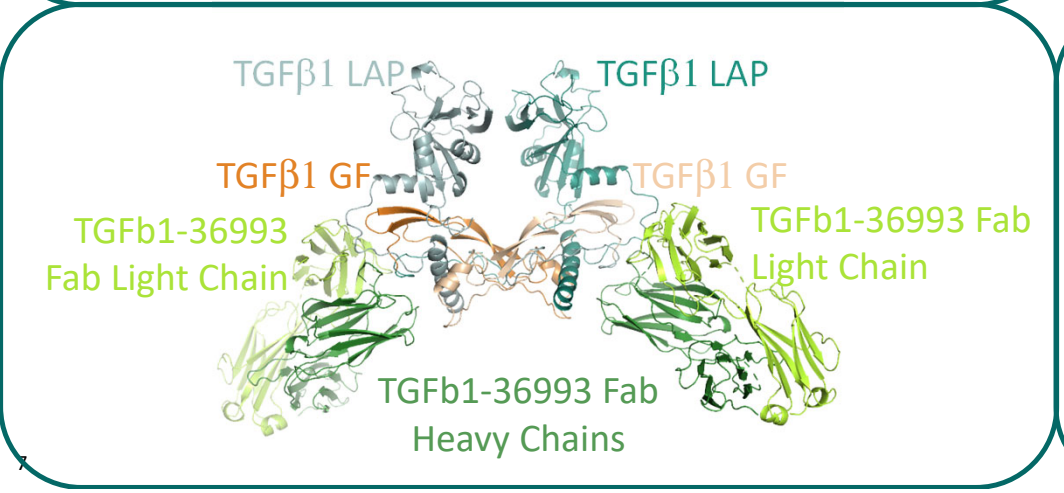
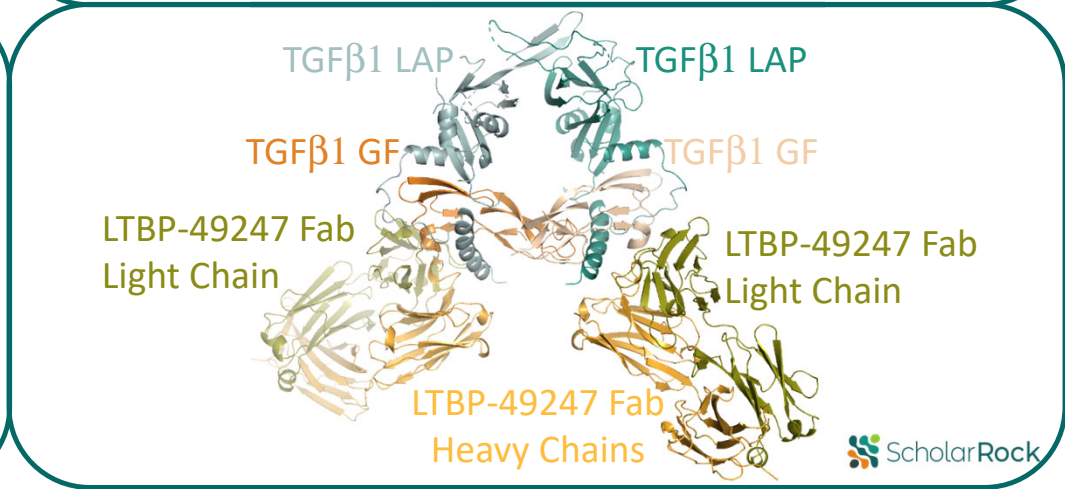
Structures of the four latent TGFβ1 inhibitor fabs in complex with the TGFβ1 small latent complex reveal distinct mechanisms of action









Integrin-mediated activation is not the only relevant mechanism for TGFβ1

Proteolytic Activation of Latent Transforming Growth Factor-β from Fibroblast-conditioned Medium

Russette M. Lyons, Jorma Keski-Oja, and Harold L. Moses

Department of Cell Biology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

The Journal of Cell Biology, Volume 106, May 1988 1659-1665

. 192, No. 2, 1993
April 30, 1993
BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Pages 940-947

MITOGENIC RESPONSE OF OSTEOBLAST CELLS TO PROSTATE-SPECIFIC ANTIGEN SUGGESTS AN ACTIVATION OF LATENT TGF-β AND A PROTEOLYTIC MODULATION OF CELL ADHESION RECEPTORS

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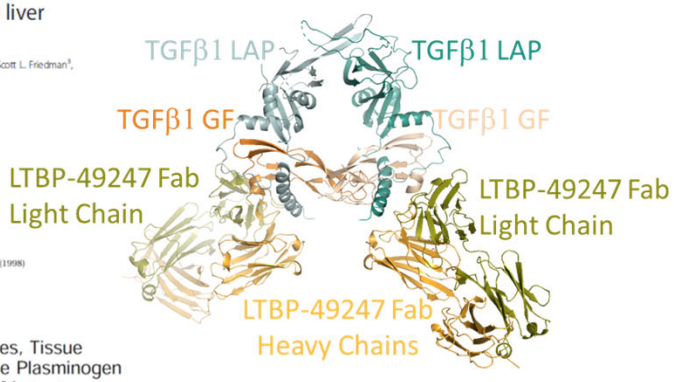
Hara et al. Fibrogenesis & Tissue Repair (2015) 8:17
DOI 10.1186/s13069-015-0034-9

Fibrogenesis & Tissue Repair

RESEARCH Open Access

L[59] TGF-β LAP degradation products serve as a promising blood biomarker for liver fibrogenesis in mice

Mitsuko Hara[1], Ikuyo Inoue[1], Yuta Yamazaki[1], Akiko Kirita[1], Tomokazu Matsuura[2], Scott L. Friedman[3], Daniel B. Rifkin[4,5] and Soichi Kojima[1*]



BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS 253, 128–134 (1998)
ARTICLE NO. RC989760

Plasmin, Substilisin-like Endoproteases, Tissue Plasminogen Activator, and Urokinase Plasminogen Activator Are Involved in Activation of Latent TGF-β_1 in Human Seminal Plasma

T. Ming Chu[1] and Elzbieta Kawinski
Department of Diagnostic Immunology Research and Biochemistry, Roswell Park Cancer Institute, New York State Department of Health, Buffalo, New York 14263

Redox-Mediated Activation of Latent Transforming Growth Factor-β1

M. H. Barcellos-Hoff and Thomas A. Dix

Life Sciences Division (M.H.B-H.), Ernest O. Lawrence Berkeley National Laboratory, University of California, Berkeley, California 94720; and Department of Pharmaceutical Sciences (T.A.D.), Medical University of South Carolina, Charleston, South Carolina 29425

RADIATION RESEARCH 166, 839–848 (2006)
0033-7587/06 $15.00

Isoform-Specific Activation of Latent Transforming Growth Factor β (LTGF-β) by Reactive Oxygen Species

Michael F. Jobling,[a] Joni D. Mott,[a] Monica T. Finnegan,[a] Vladimir Jurukovski,[a,1] Anna C. Erickson,[a] Peter J. Walian,[a] Scott E. Taylor,[a] Steven Ledbetter,[a] Catherine M. Lawrence,[a] Daniel B. Rifkin[a] and Mary Helen Barcellos-Hoff[b,2]

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CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Validation of Anticorrelated TGFβ Signaling and Alternative End-Joining DNA Repair Signatures that Predict Response to Genotoxic Cancer Therapy

Ines Guix[1], Qi Liu[1], Miquel Angel Pujana[2], Patrick Ha[3], Josep Piulats[2], Isabel Linares[2], Ferran Guedea[2], Jian-Hua Mao[3], Ann Lazar[6,7], Jocelyn Chapman[6,9], Sue S. Yom[1,8], Alan Ashworth[9], and Mary Helen Barcellos-Hoff[1,8]

Mitochondrial Reactive Oxygen Species Regulate Transforming Growth Factor-β Signaling

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Manu Jain[1,2], Stephanie Rivera[1], Elena A. Monclus[1], Lauren Synenki[1], Aaron Zirk[1], James Eisenbart[1], Carol Feghali-Bostwick[3], Gokhan M. Mutlu[1,4], G. R. Scott Budinger[1], and Navdeep S. Chandel[1,4]

From the [4]*Division of Pulmonary and Critical Care, Department of Medicine, and the* [5]*Department of Cell and Molecular Biology, Northwestern University Medical School, Chicago, Illinois 60611 and the* [3]*Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, and the Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania 15213*

Asbestos-derived reactive oxygen species activate TGF-β_1

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Oxidative stress contributes to the induction and persistence of TGF-β1 induced pulmonary fibrosis

Ye Cui[a,b,c], Jennifer Robertson[b], Shyam Maharaj[b,c], Lisa Waldhauser[b], Jianzhao Niu[a], Jifeng Wang[a], Laszlo Farkas[c,d], Martin Kolb[c,d], Jack Gauldie[b,c]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Loss of TGFβ signaling increases alternative end-joining DNA repair that sensitizes to genotoxic therapies across cancer types

Qi Liu[1,*], Luis Palomero[2], Jade Moore[1], Ines Guix[1], Roderic Espín[2], Alvaro Aytés[2], Jian-Hua Mao[3], Amanda G. Paulovich[4], Jeffrey R. Whiteaker[4], Richard G. Ivey[4], George Iliakis[5], Daxian Luo[5], Anthony J. Chalmers[6], John Murnane[3], Miquel Angel Pujana[2†], Mary Helen Barcellos-Hoff[1†]

Role of Reactive Oxygen Species in TGF-β1–Induced Mitogen-Activated Protein Kinase Activation and Epithelial-Mesenchymal Transition in Renal Tubular Epithelial Cells

Dong Young Rhyu,*† Yanqiang Yang,*‡ Hunjoo Ha,*§ Geun Taek Lee,* Jae Sook Song,* Soo-taek Uh,* and Hi Bahl Lee*

*Hyonam Kidney Laboratory, Soon Chun Hyang University, Seoul, Korea; †Department of Medicinal Plant Resources, Mokpo National University, Jeonnam, Korea; ‡National Institute of Nephrology, First Affiliated Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China; and §Ewha Womans University College of Pharmacy, Seoul, Korea

The Latent Form of TGFβ_1 is Induced by TNFα Through an ERK Specific Pathway and is Activated by Asbestos-Derived Reactive Oxygen Species *In Vitro* and *In Vivo*

Deborah E. Sullivan, MaryBeth Ferris, Derek Pociask & Arnold R. Brody

Contents lists available at ScienceDirect
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journal homepage: www.elsevier.com/locate/redox

Review Article

Reciprocal regulation of TGF-β and reactive oxygen species: A perverse cycle for fibrosis

Rui-Ming Liu*, Leena P. Desai

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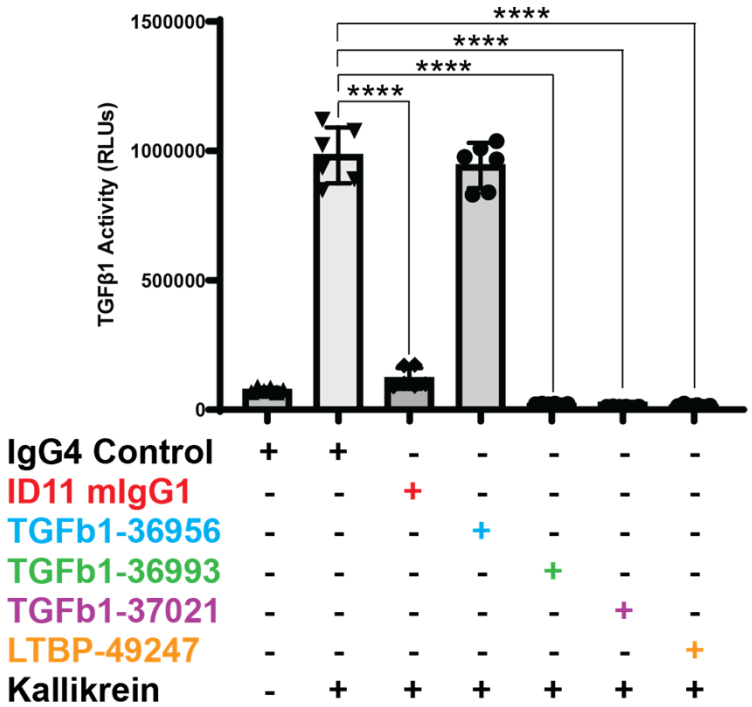
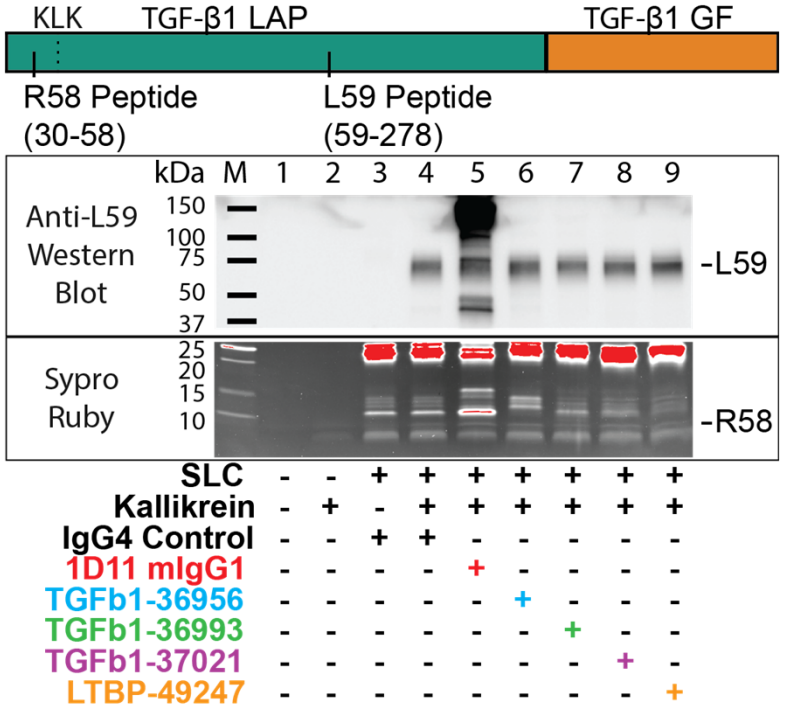
Antibodies with stabilizing epitopes can inhibit Kallikrein mediated activation of TGFβ1





- Epitopes that contact both the Latency Associated Peptide (LAP) and Growth Factor (GF) stabilize or clamp the complex together and prevent signaling, despite apparent cleavage.
- The integrin competitive epitope cannot inhibit this activation.

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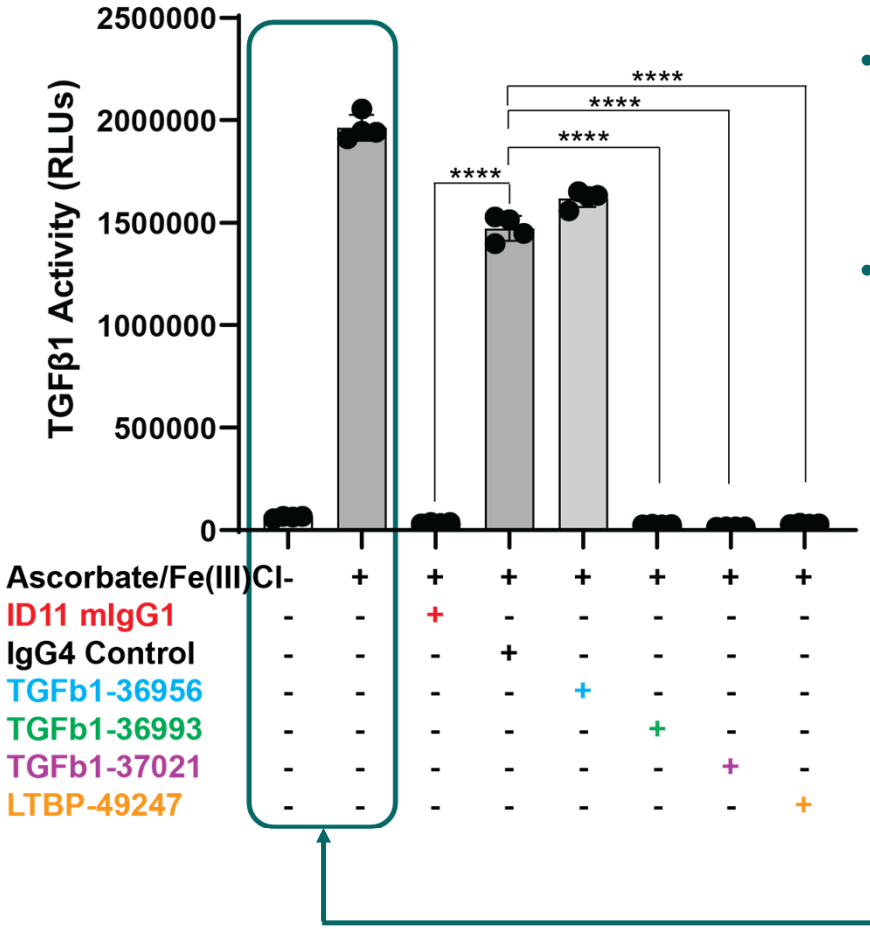
Antibodies with stabilizing epitopes can inhibit Reactive Oxygen Species (ROS)-mediated activation of TGFβ1



- Question: Does treatment with ROS cause the latent complex to dissociate?
- Take these samples and inject onto Size Exclusion Chromatography (SEC) to investigate the integrity of the complex

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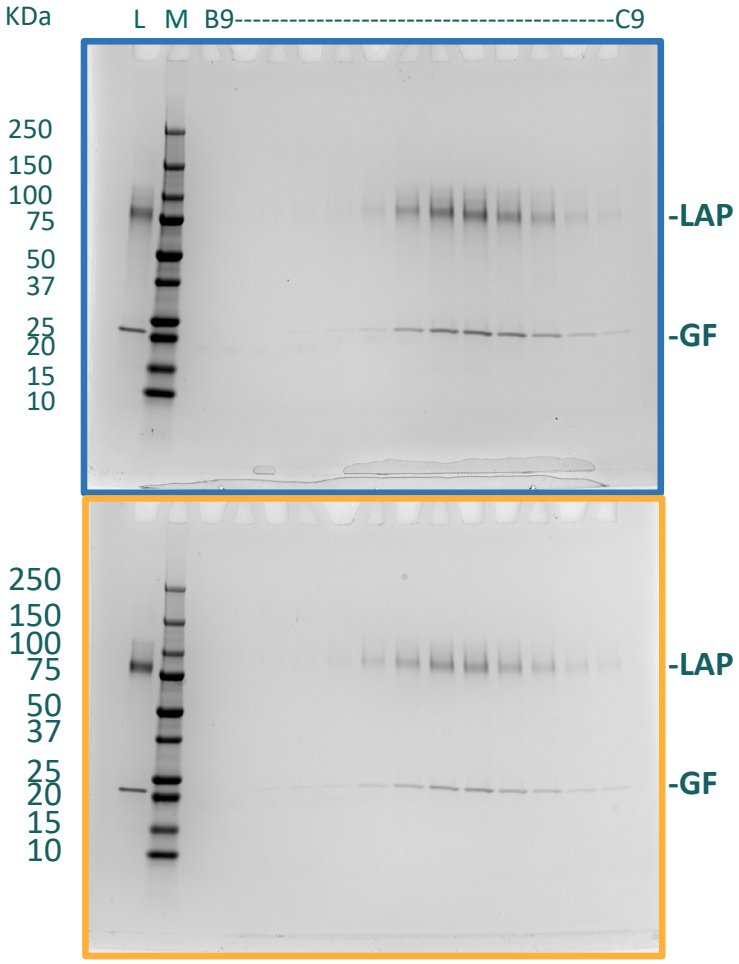
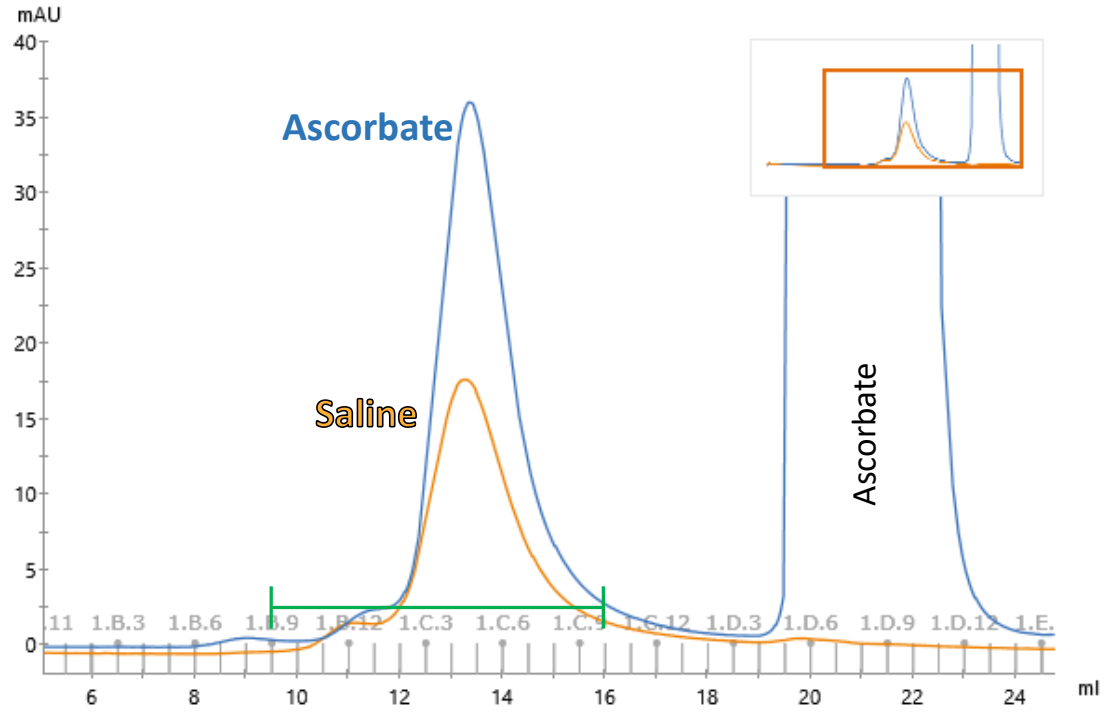
ROS treatment of TGFβ1 does not cause the LAP and GF to dissociate during size exclusion chromatography





- **Simple explanation:** The TGFβ1 complex is still latent entering the cell assay but is rendered susceptible to some cellular factor (e.g., protease).
- **Alternative hypothesis:** TGFβ1 undergoes a ROS mediated conformational change that allows signaling within the complex (e.g., Campbell et al 2020).

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Conclusions

- Scholar Rock platform incorporates structural characterization of our antibodies to gain detailed insights into MOA and selectivity
- Epitopes that bind both the LAP and GF, stabilizing the latent complex together, can prevent protease- and ROS-mediated latent TGFβ1 activation; whereas the integrin competitive epitope cannot.
- The inhibitory epitope for our immuno-oncology lead, SRK-181, is a stabilizing epitope that can inhibit all three modes of activation (integrin, protease, and ROS) in all presentation contexts.
  - Would expect this type of inhibitory antibody to be one that supplements radiation therapy
- The LTBP context selective epitope is also a stabilizing epitope that can inhibit all three modes of activation (integrin, protease, and ROS) but limited to TGFβ1 presented by LTBP1 and 3.
  - Please check out our recent Science Signaling publication on this molecule, including many more details about the context selectivity and preclinical target engagement and efficacy in rodent models.

Thank you to the organizers and for your attention!

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