



SCHOLAR ROCK

From New Insights to New Medicines

December 2018

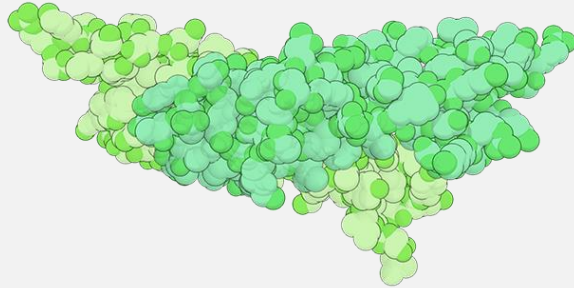
Disclaimers

Various statements in this presentation concerning Scholar Rock's future expectations, plans and prospects, 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 clinical trials for its product candidates, its product candidate selection and development timing, its disease indication selection timing, its management team capabilities, and the ability of SRK-015 to affect the treatment of patients suffering from SMA either as a monotherapy or in conjunction with the current standard of care, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. The use of words such as "may," "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. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including, without limitation, Scholar Rock's ability to provide the financial support and resources necessary to identify and develop product candidates on the expected timeline, competition from others developing products for similar uses, Scholar Rock's ability to obtain, maintain and protect its intellectual property, Scholar Rock's dependence on third parties for development and manufacture of product candidates including to supply any clinical trials, and 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 as well as those risks more fully discussed in the section entitled "Risk Factors" in the Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, which is on file with the Securities and Exchange Commission, 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. Scholar Rock explicitly disclaims any obligation to update any forward-looking statements unless required by law.

Nature's Growth Factor Activation Machinery

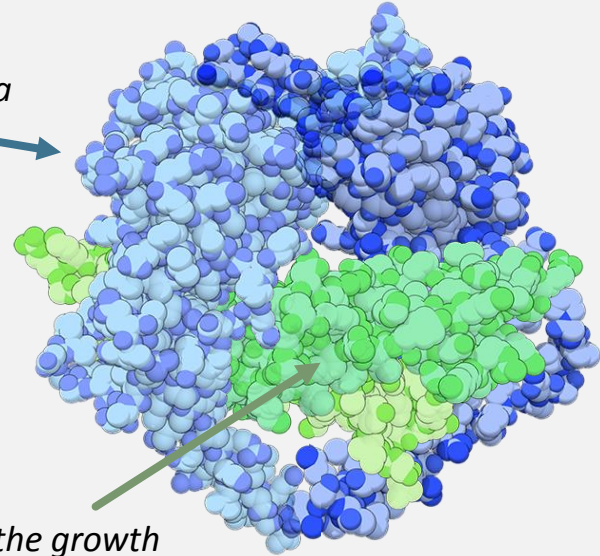
Mature TGF β 1

Active form of the growth factor



TGF β 1 Precursor Complex

TGF β 1 propeptide which forms a "cage"



Cage renders the growth factor inactive or "latent"

TGF β Superfamily: More than 30 Related Growth Factors that Mediate Diverse Biological Processes

Scholar Rock's Solution to Traditional Challenges

Traditional Challenges:

- Focused on inhibiting the growth factor after activation and systemic release
- Have been limited by:
 - Structural similarities
 - Overlapping sets of related receptors
 - Diverse and overlapping physiological roles

Target Signaling Proteins at the Cellular Level
(Based on Scholar Rock's Structural Biology Insights)

Nature's Way of Regulating Growth Factor Activity

High Selectivity

Localization of Effect

Well-established Modality (Monoclonal Antibodies)

Proprietary Platform to Target Growth Factor Activation

Design and Purification of Challenging Proteins
(e.g. latent growth factor complexes)

Proprietary Assays
that Recapitulate
Nature's Activation
In Vitro

SCHOLAR ROCK DISCOVERY PLATFORM

Sophisticated Selection Strategies Utilizing
Recombinant Antibody Libraries

**Broad IP Portfolio
Covering
Compositions and
Methods**

Exemplified by

- US Patent 9,758,576
- Issued in September 2017
(expiry in 2034)
- Covers monoclonal antibodies
that inhibit the activation of the
myostatin precursor

Robust Pipeline Portfolio

PROGRAM		STAGE OF DEVELOPMENT					STATUS	
Target	Indication	Late-Stage Discovery	Preclinical	Phase 1	Phase 2	Phase 3	Worldwide Rights	Next Anticipated Milestone
SRK-015 Program								
Latent Myostatin	Spinal Muscular Atrophy							Phase 1 Trial Ongoing
Latent Myostatin	Additional Myostatin-Related Disorders							1H:2019 – Identify Next Indication
TGFβ1 Program								
Context-Independent								
Latent TGFβ1	Oncology/Immuno-oncology; Fibrosis							1H:2019 – Nominate Product Candidate
Context-Dependent								
Latent TGFβ1 / GARP	Oncology/Immuno-oncology						<i>Janssen Biotech, Inc.</i>	
Latent TGFβ1 / GARP & LRRC33	Oncology/Immuno-oncology							
Latent TGFβ1 / LRRC33	Oncology/Immuno-oncology							
Latent TGFβ1 / LTBP1 & LTBP3	Fibrosis							
BMP6 Program								
BMP6 Signaling Pathway	Anemia							

SRK-015: Inhibitor of Myostatin Activation

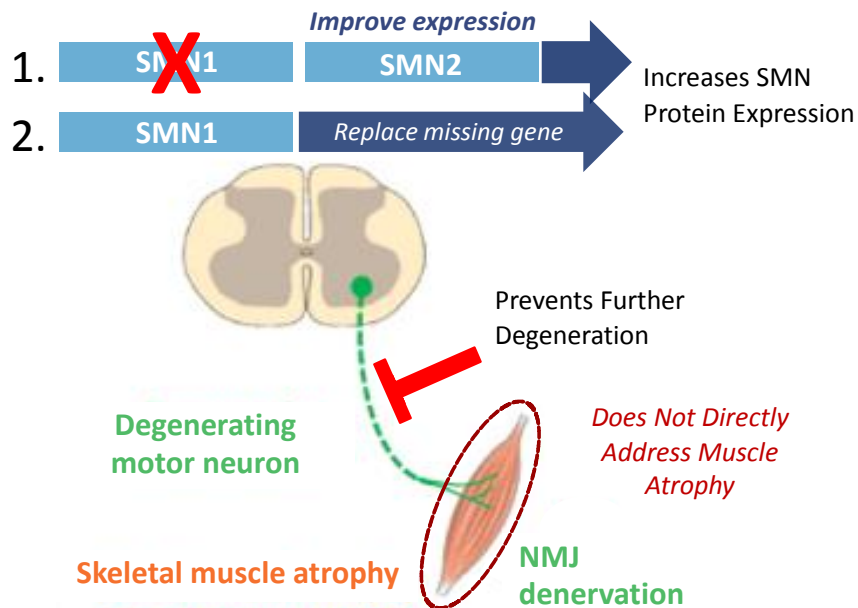
Potential First Muscle-Directed Therapy for SMA



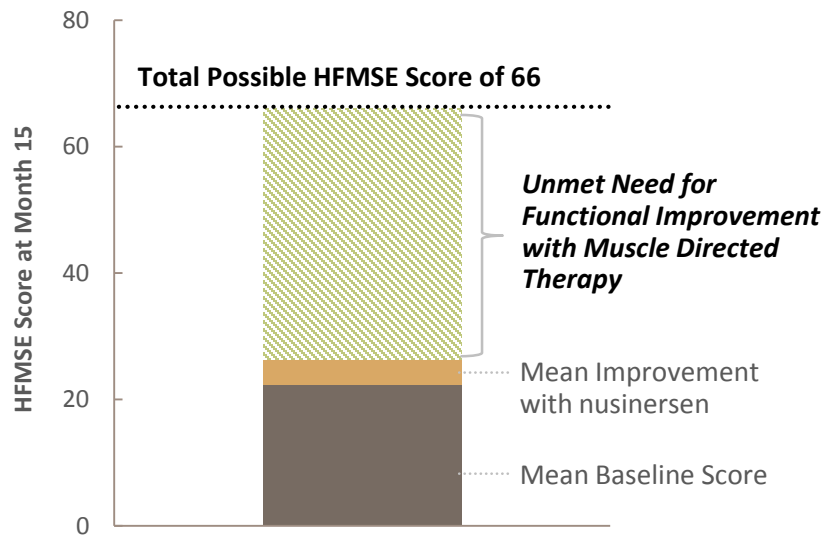
SCHOLAR ROCK

SMN Upregulators Do Not Directly Address Muscle Atrophy

Significant Unmet Need Remains Despite Current Therapeutic Strategies



Muscle Function in SMA (Human) *Hammersmith Functional Motor Scale Expanded (HFMSE)*



Mean improvement in HFMSE score experienced by patients with later-onset SMA in the Phase 3 CHERISH clinical trial of nusinersen.

Adapted from images that were courtesy of the SMA Foundation

SRK-015: Muscle-Directed Approach to Treating SMA

Vertebrates lacking the myostatin gene are healthy and display increased muscle mass and strength



- Myostatin is a genetically-validated, negative regulator of muscle mass expressed in skeletal muscle tissue
- There has been high interest from pharma as a potential drug target
- Clinical trial results with traditional systemic inhibitors of mature myostatin (or its receptor) have been mixed

Differentiated approach with SRK-015:

Inhibition of myostatin activation to potentially improve muscle function

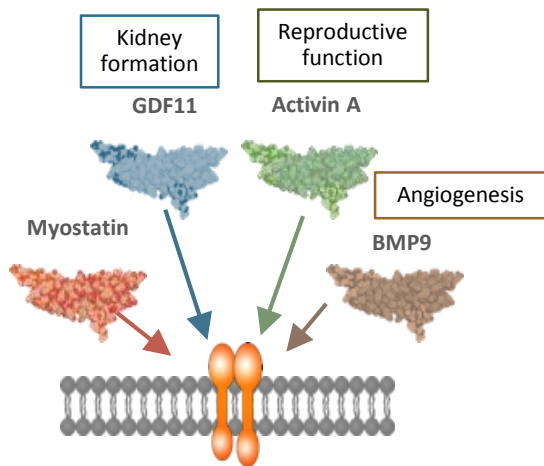
SRK-015: Aligning Therapeutic Approach with Myostatin Biology

Optimal Setting for Myostatin Inhibition		Key Characteristics of Spinal Muscular Atrophy (SMA)
Younger population		Genetic disorder with onset in childhood
Muscle disease with at least partially intact innervation		Incomplete loss of motor neurons
Need for increase in fast-twitch muscle fibers		Substantial deficit in fast-twitch fibers
Clinical trial endpoint driven by fast-twitch fiber function		Fast-twitch fiber function; prominent role in SMA outcome measures

Traditional Approaches Can Raise Significant Safety Concerns

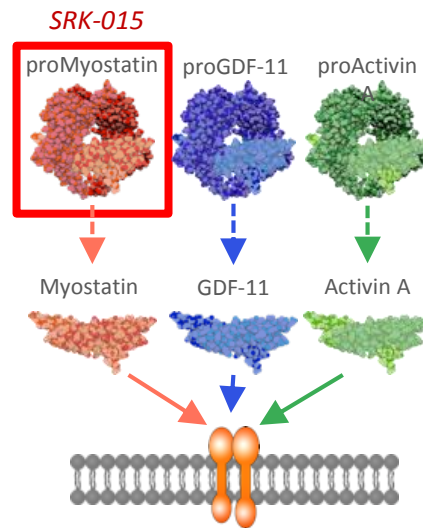
Traditional Approaches Lack Selectivity

- Most inhibitors of active myostatin also inhibit GDF11 and may inhibit other growth factors as well
- Antibodies to ActRIIb and ligand trap approaches inhibit signaling of multiple ligands



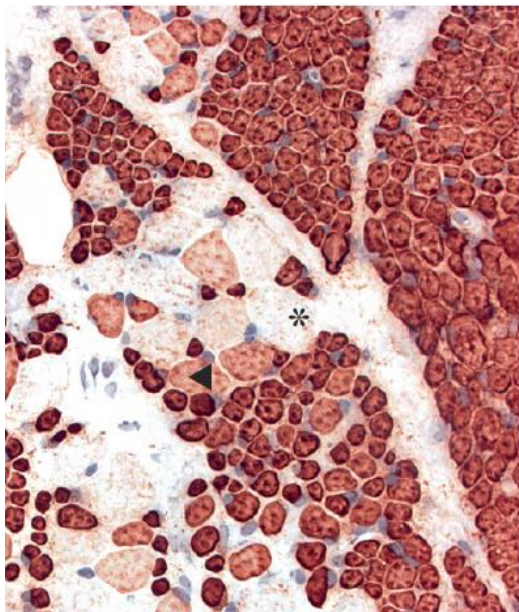
Scholar Rock Approach

Exquisite Selectivity By Targeting Precursor Form of Myostatin



Fast-Twitch Muscle Fibers May Be Preferentially Benefited by SRK-015

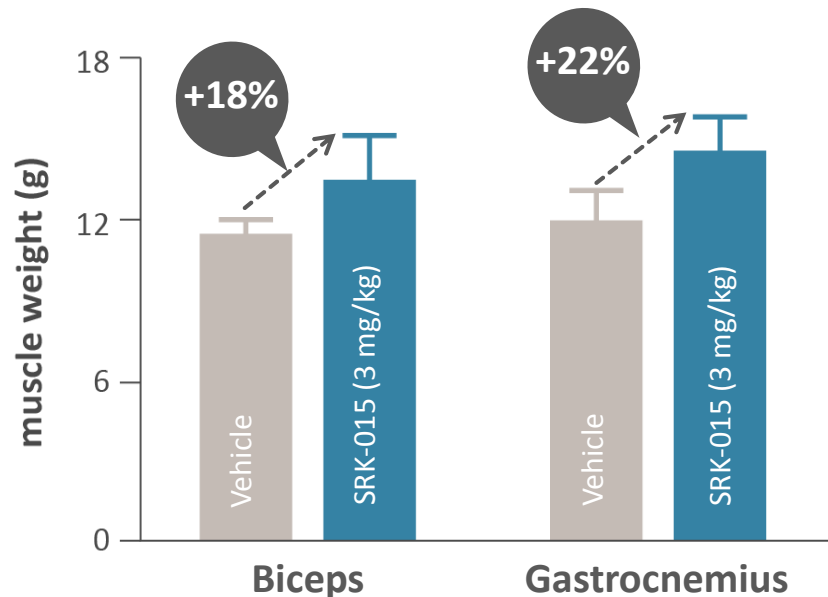
Muscle From 5-Year Old SMA Type II Patient



- Muscle is comprised of both slow-twitch and fast-twitch fibers
- Fast-twitch fibers significantly atrophy in patients with SMA

Dubowitz, et al., 2013. *Neurogenic Disorders. Muscle Biopsy, A Practical Approach.*

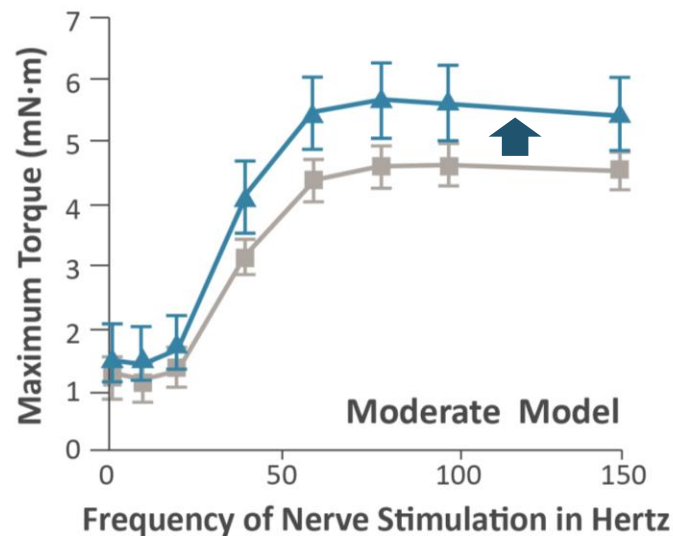
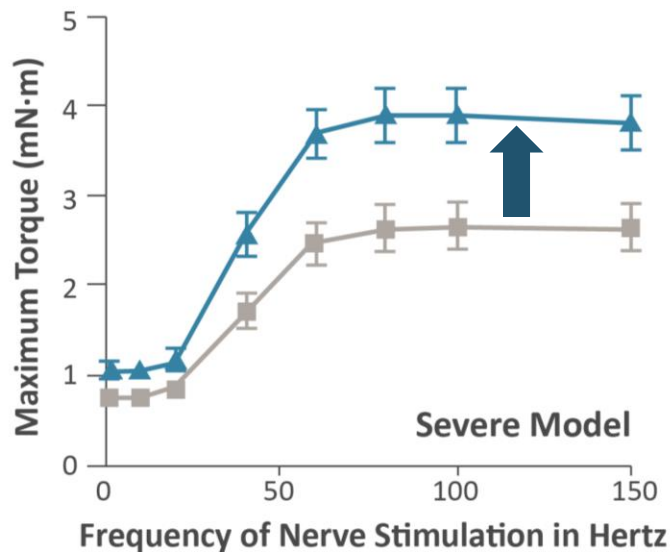
Healthy Non-Human Primate (Cyno) Pronounced Effect on Fast-Twitch Muscle



Six cynomolgus animals per group were treated once weekly with vehicle control or SRK-015 for 8 weeks and assessed after an additional 5 weeks

SRK-015 Demonstrates Potential Benefits Across SMA Severities

Genetic Model of SMA (“ $\Delta 7$ Mouse”) Demonstrate Improved *In Vivo* Muscle Force Generation *Strength of Plantarflexor Muscle Group*



- ▲ SMN upregulator + SRK-015
- SMN upregulator only

SRK-015 Phase 1 Trial Design

Design	• Double-blind, placebo-controlled • 3:1 randomization • Single- and multiple-ascending dose
Subjects	• Adult healthy volunteers (ages 18-55) • Anticipate enrolling ~60 subjects total
Key Objectives	• Safety and tolerability of SRK-015 IV • PK/PD • Immunogenicity
Status	• Interim results expected 1Q19

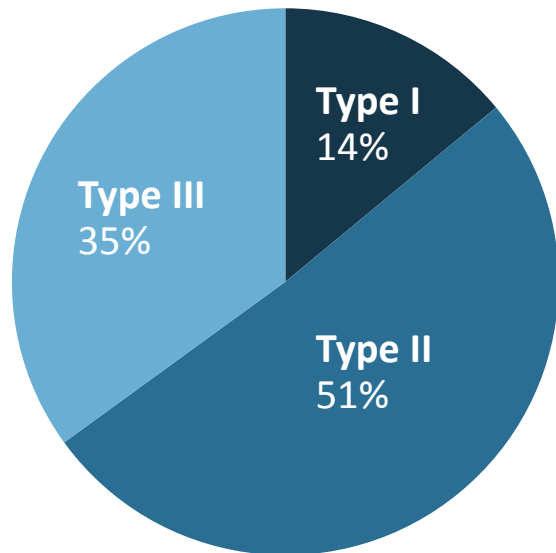


Initiate Phase 2
POC study in
SMA in 1Q19

SRK-015 Opportunity in Spinal Muscular Atrophy

Overall Prevalence of 30,000-35,000 in U.S. and Europe

RELATIVE PREVALENCE AMONG
PATIENTS LIVING WITH SMA



Type I:

- Infant-onset; often fatal

Type II and non-ambulatory type III:

- Later-onset but still early childhood
- Severe deficits in motor function

*Potential to use
SRK-015 in
conjunction with
current standard
of care*

Ambulatory type III:

- Limited mobility and substantial morbidity

*Potential to use
SRK-015 as
monotherapy*

Type IV:

- Population not well-characterized

Recent Achievements and Upcoming Milestones

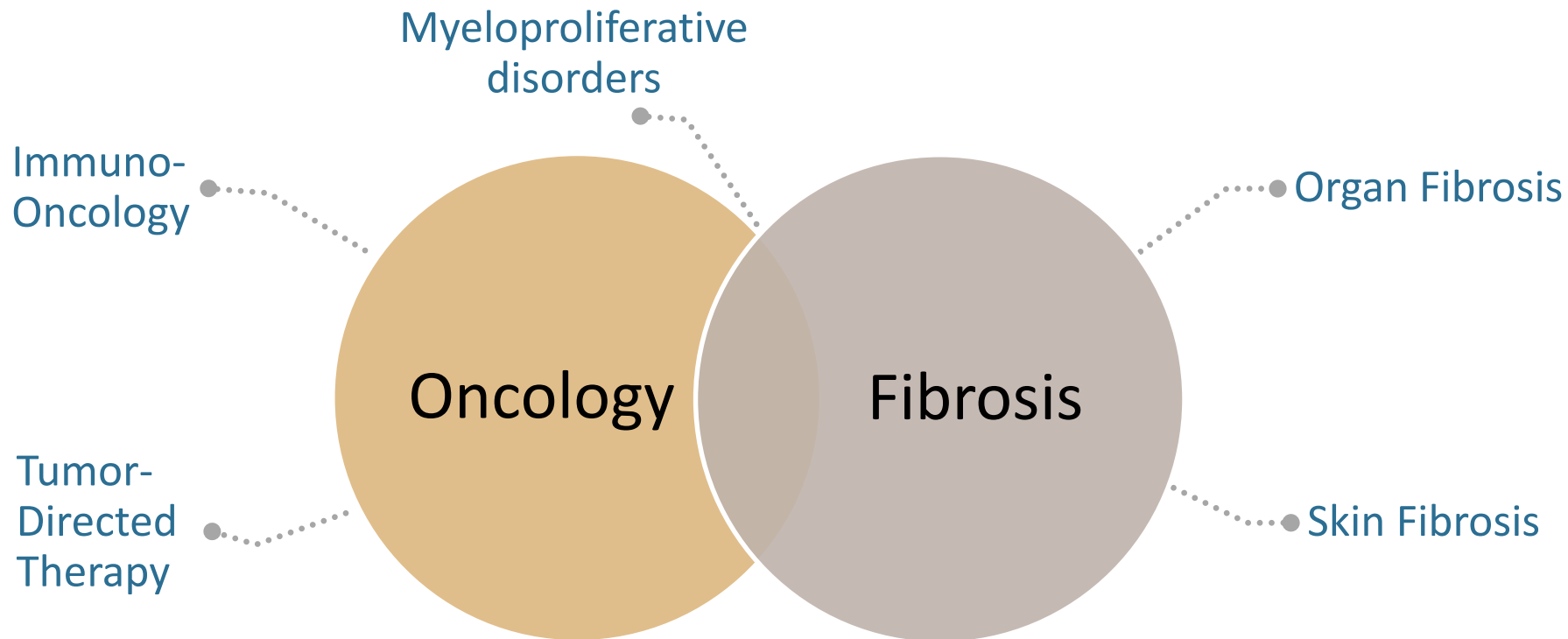
- ✓ FDA granted Orphan Drug Designation for the treatment of SMA
- ✓ EMA's COMP adopted positive opinion on Orphan Drug Designation for the treatment of SMA
- ✓ Completed IND-enabling toxicology studies
- ✓ IND in SMA submitted to FDA in March and cleared in April 2018
- ✓ Published preclinical data in *Human Molecular Genetics*⁽¹⁾ demonstrating the therapeutic benefits of inhibiting myostatin in mouse models of SMA
- ✓ Initiated Phase 1 clinical trial in healthy volunteers in May 2018
- ❑ Interim results from Phase 1 clinical trial in healthy volunteers in 1Q19
- ❑ Initiate Phase 2 proof-of-concept study in patients with SMA in 1Q19
 - ❑ Initial functional results from Phase 2 proof-of-concept study expected in 2H19
- ❑ Identify next indication for SRK-015 in 1H19

TGF β 1: Significant Opportunities in Oncology/Immuno-oncology and Fibrosis



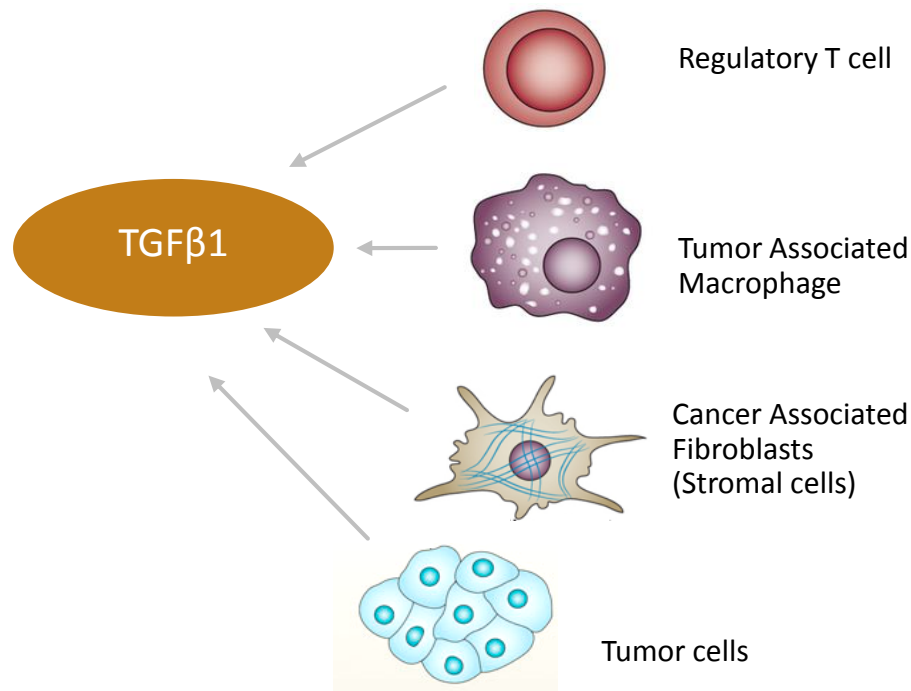
SCHOLAR ROCK

TGFβ1 Plays Central Role in Multiple Diseases with Unmet Need



Inhibition of TGFβ1: Multipronged Approach for Immuno-Oncology

TGFβ1 is a key driver of immune system evasion by cancer cells



Nature (on-line), Feb. 14, 2018

doi:10.1038/nature25501

TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells

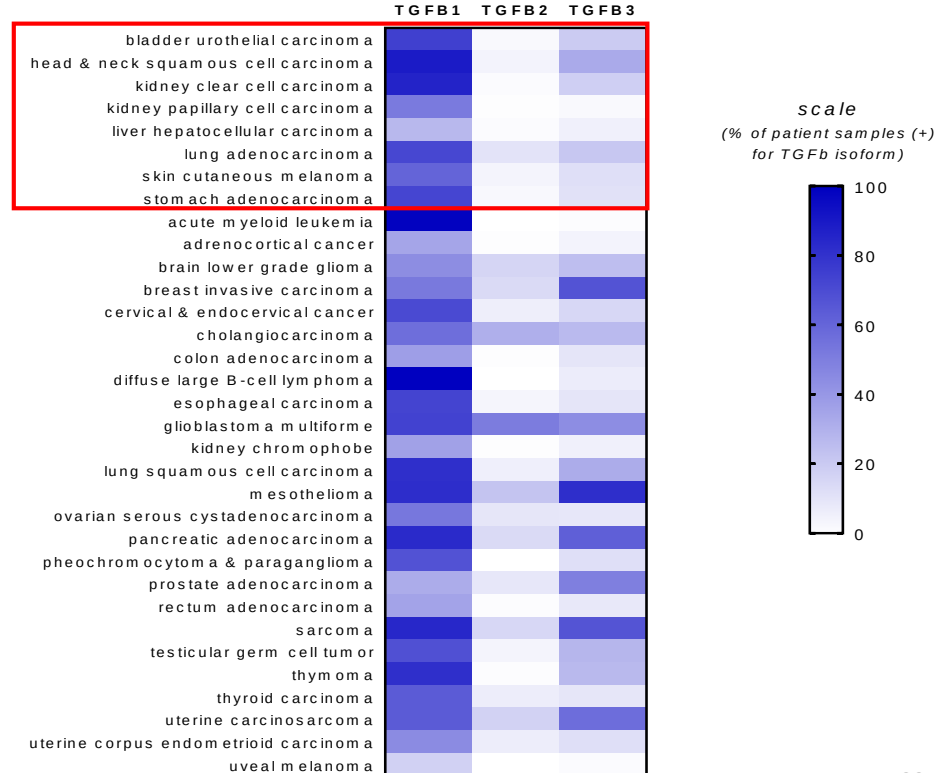
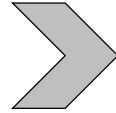
Sanjeev Mariathasan^{1*}, Shannon J. Turley^{1*}, Dorothee Nickles^{1*}, Alessandra Castiglioni¹, Kobe Yuen¹, Yulei Wang¹, Edward E. Kadel III¹, Hartmut Koeppen¹, Jillian L. Astarita¹, Rafael Cubas¹, Suchit Jhunjhunwala¹, Romain Banchereau¹, Yagai Yang¹, Yinghui Guan¹, Cecile Chalouni¹, James Ziai¹, Yasin Senbabaoglu¹, Stephen Santoro¹, Daniel Sheinson¹, Jeffrey Hung¹, Jennifer M. Giltman¹, Andrew A. Pierce¹, Kathryn Mesh¹, Steve Lianoglou¹, Johannes Riegler¹, Richard A. D. Carano¹, Pontus Eriksson², Mattias Höglund², Loan Somarriba³, Daniel L. Halligan³, Michiel S. van der Heijden⁴, Yohann Loriot⁵, Jonathan E. Rosenberg⁶, Lawrence Fong⁷, Ira Mellman¹, Daniel S. Chen¹, Marjorie Green¹, Christina Derleth¹, Gregg D. Fine¹, Priti S. Hegde¹, Richard Bourgon¹ & Thomas Powles⁸

- Pathway analysis points to TGFβ1 as major determinant of resistance to anti-PD-L1 (atezolizumab)
- TGFβ1 creates 'immune excluded' tumor microenvironment
- Anti-TGFβ antibody enhances anti-PDL1 treatment response in syngeneic EMT-6 tumor model

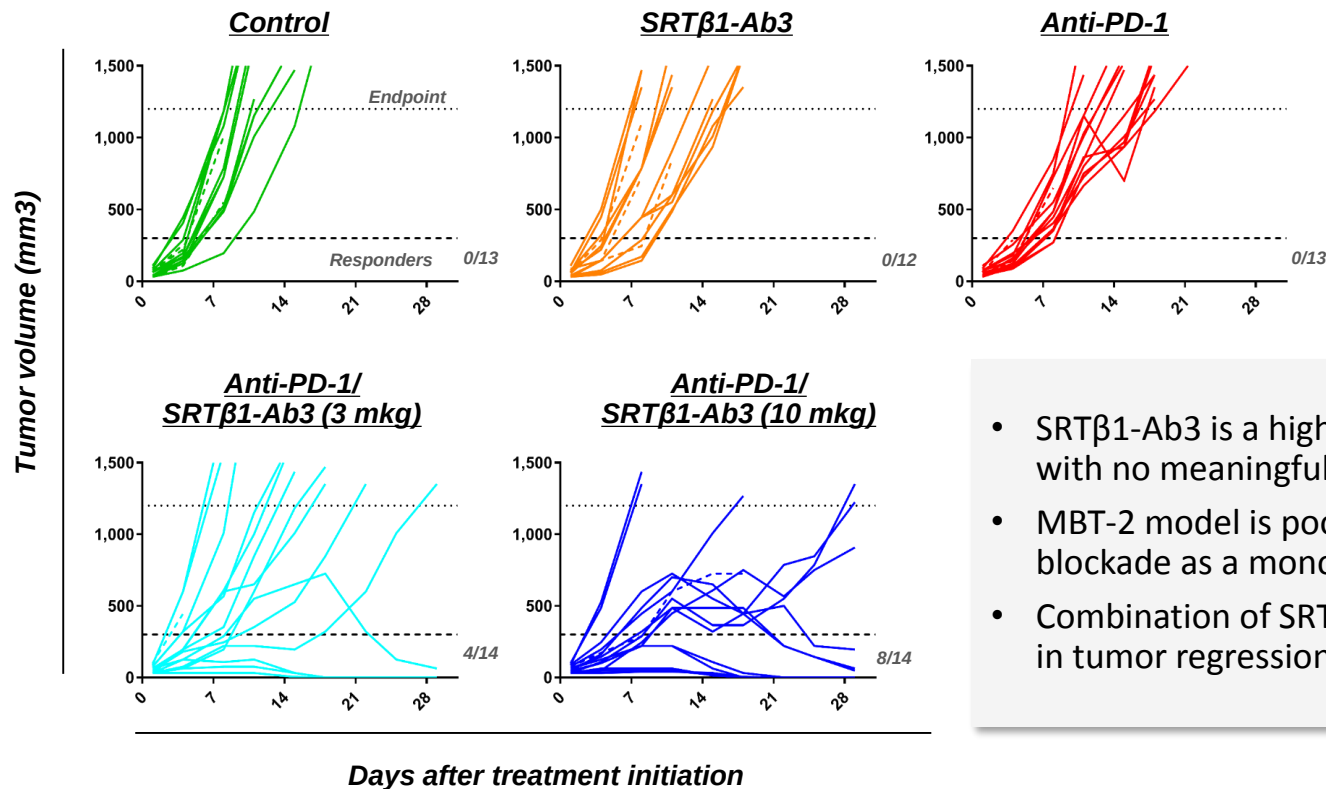
TGFβ1 is the Predominant Isoform in Most Human Tumors

The Cancer Genome Atlas RNAseq analysis: >10,000 samples spanning 33 tumor types

- TGFβ1 prevalent in human cancers for which checkpoint therapies are approved
- Expression data for most tumor types suggest that TGFβ signaling mainly driven by TGFβ1



TGF β 1 Blockade with SRT β 1-Ab3 Renders MBT-2 Tumors Susceptible to Anti-PD1 Therapy

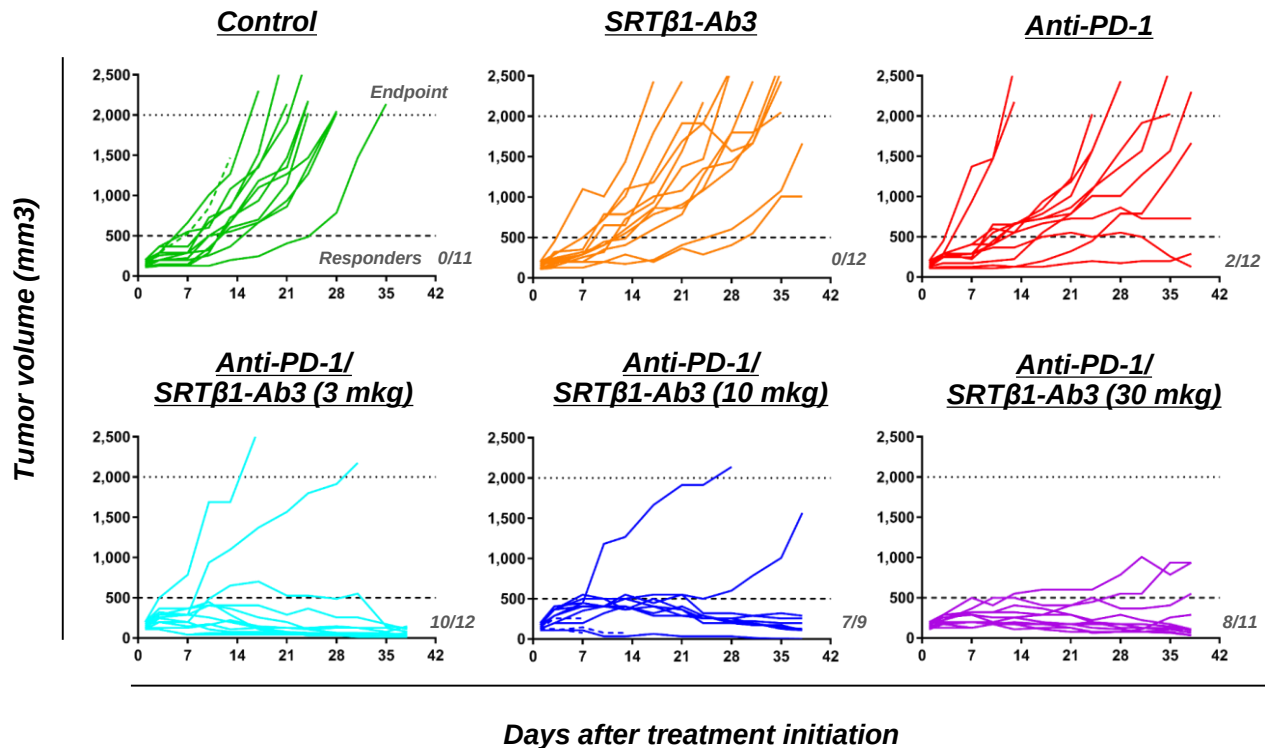


Dosing initiated when tumors reached 30-80 mm³

Treatment with RMP1-14 anti-PD1 (5mg/kg twice weekly) and/or SRT β 1-Ab3 (once weekly at indicated dose)

- SRT β 1-Ab3 is a highly specific inhibitor of TGF β 1 with no meaningful binding to TGF β 2/TGF β 3
- MBT-2 model is poorly responsive to PD-1 blockade as a monotherapy
- Combination of SRT β 1-Ab3 and anti-PD1 resulted in tumor regression or tumor control

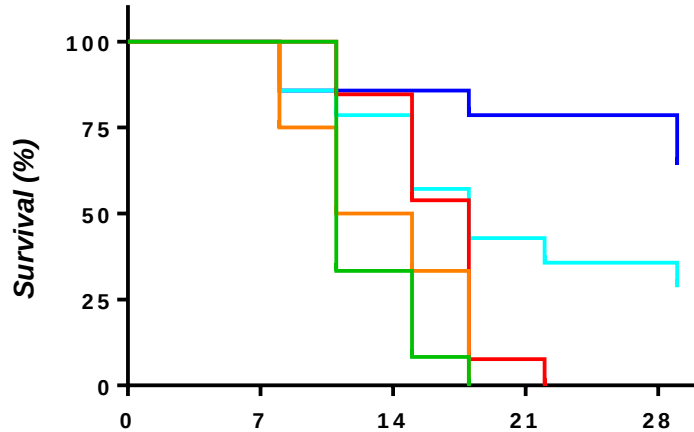
Anti-TGF β 1 Combination with PD-1 blockade is Effective in Cloudman S91 Melanoma Model



- Cloudman S91 model is poorly responsive to PD-1 blockade as a monotherapy
- Combination of SRT β 1-Ab3 and anti-PD1 resulted in tumor regression or tumor control
- Study ongoing

SRTβ1-Ab3 Combined with Anti-PD1 Therapy Leads to Significant Survival Benefit

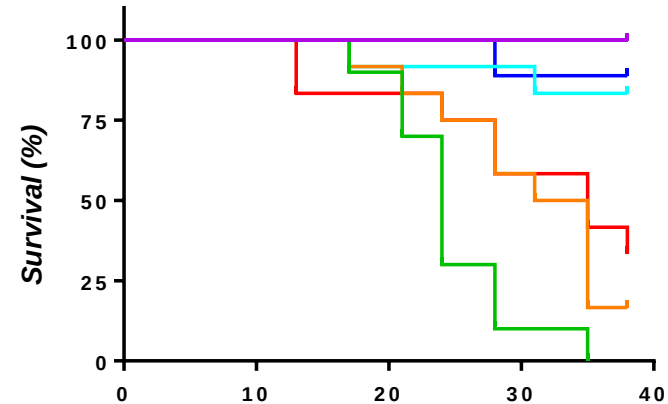
MBT-2 Bladder Cancer Tumor Model



- Control (30 mkg qwk)
- SRTβ1-Ab3 (10 mkg qwk)
- anti-PD-1 (5 mkg twice weekly)
- anti-PD-1 + SRTβ1-Ab3 (3 mkg qwk)
- anti-PD-1 + SRTβ1-Ab3 (10 mkg qwk)

*** P<0.001 Log-rank (Mantel-Cox) test

Cloudman S91 Melanoma Tumor Model (study ongoing)



- Control (30 mkg qwk)
- SRTβ1-Ab3 (30 mkg qwk)
- anti-PD-1 (5 mkg twice weekly)
- anti-PD-1 + SRTβ1-Ab3 (3 mkg qwk)
- anti-PD-1 + SRTβ1-Ab3 (10 mkg qwk)
- anti-PD-1 + SRTβ1-Ab3 (30 mkg qwk)

* P<0.05 Log-rank (Mantel-Cox) test

*** P<0.001

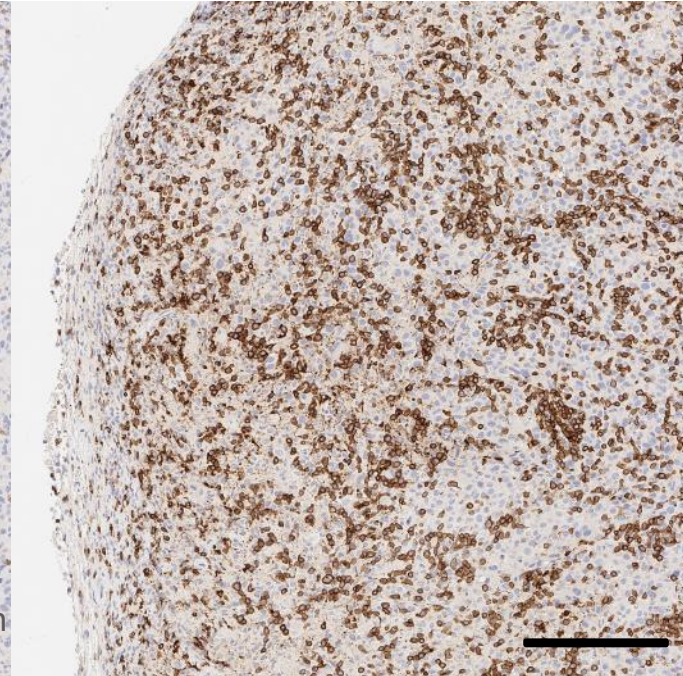
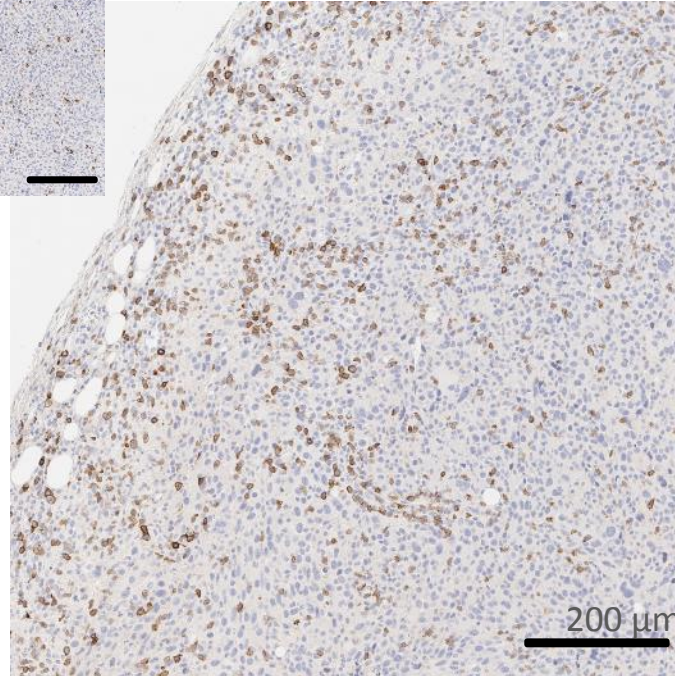
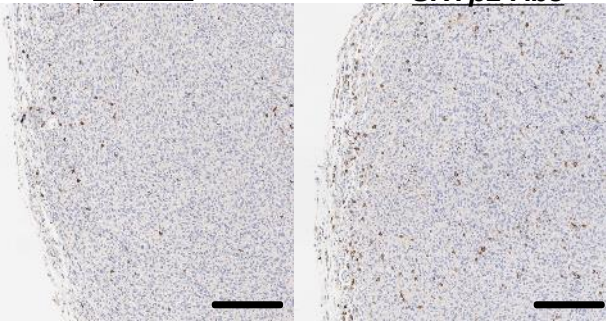
SRTβ1-Ab3 Combination Therapy Enables Infiltration and Expansion of CD8⁺ T cells in Tumors

Control

SRTβ1-Ab3

Anti-PD-1

Anti-PD-1/
SRTβ1-Ab3 (10 mkg)



IHC of MBT-2 tumors at day 10

- Marked increase in frequency of CD8⁺ T cells within the tumor
- Consistent with flow cytometry data at day 13

TGFβ1 Isoform Specificity of SRTβ1-Ab3 Results in Improved Preclinical Toxicity Profile

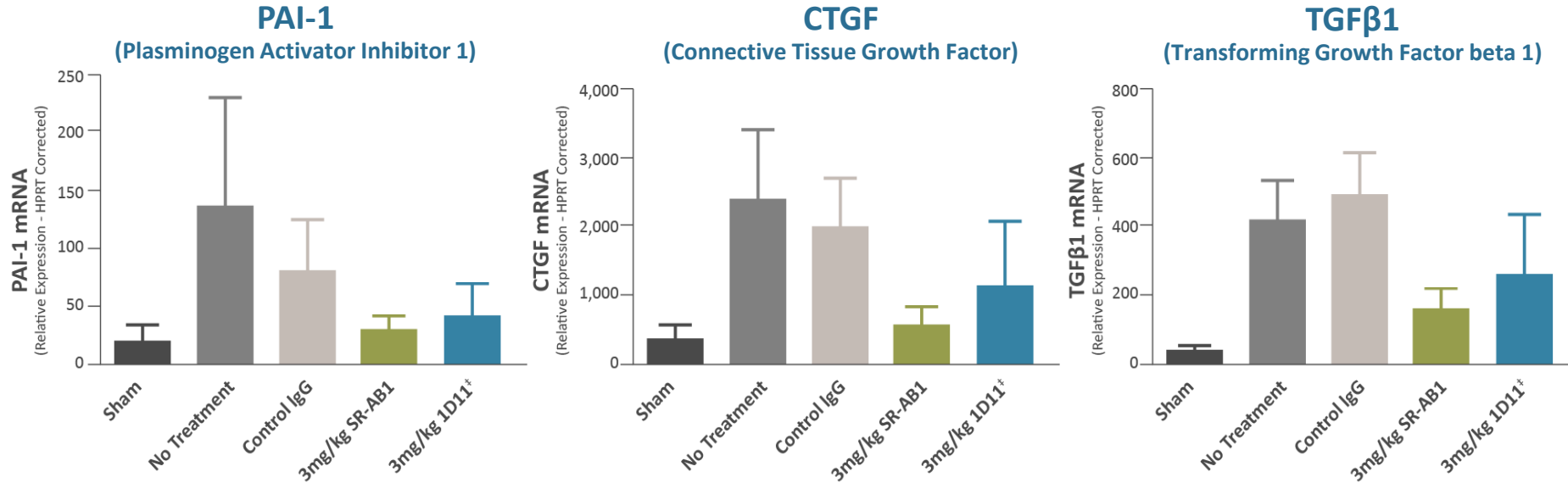
Repeat dose pilot toxicology study in adult female Sprague Dawley rats

Microscopic observations in heart	Control				LY2109761				PanTGFβAb				SRTβ1-Ab3												Legend	
	vehicle				300 mg/kg				30 mg/kg				10 mg/kg				30 mg/kg				100 mg/kg					
	iv, qwk x 4				po, qd x 8				iv, 1 dose				iv, qwk x 4				iv, qwk x 4				iv, qwk x 4					
Valvulopathy																										Unremarkable
Atrium - Mixed cell infiltrate																										Minimal
Myocardium - Degeneration/necrosis																										Slight
Myocardium - Hemorrhage																										Moderate
Myocardium - Mixed cell infiltrate, base																										
Coronary artery - Necrosis with inflammation																										
Cardiomyocyte - Necrosis/inflammatory cell infiltrate																										

- Animals dosed with pan-TGFβ inhibitors, LY2109761 (inhibitor of ALK5, common TGFβ receptor kinase) or pan-TGFβ antibody, exhibited expected cardiac findings based on published data
- Exposure as assessed by SRTβ1-Ab3 serum concentration reached 2,300 µg/ml following 4 weekly doses of 100 mg/kg
- No SRTβ1-Ab3 related adverse effects were noted up to 100 mg/kg per week
- No cardiotoxicities (valvulopathy) were noted with SRTβ1-Ab3
- No observed adverse effect level (NOAEL) for SRTβ1-Ab3 was the highest dose evaluated (100 mg/kg per week), suggesting that the maximally tolerated dose (MTD) could be >100 mg/kg per week

TGF β is a Central Driver of Fibrotic Disease

Acute Kidney Fibrosis Model (mouse UUO): Gene Expression

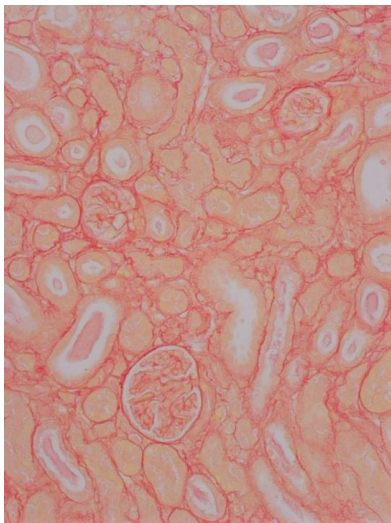


[†]1D11 is an inhibitor of all three isoforms of mature TGF β

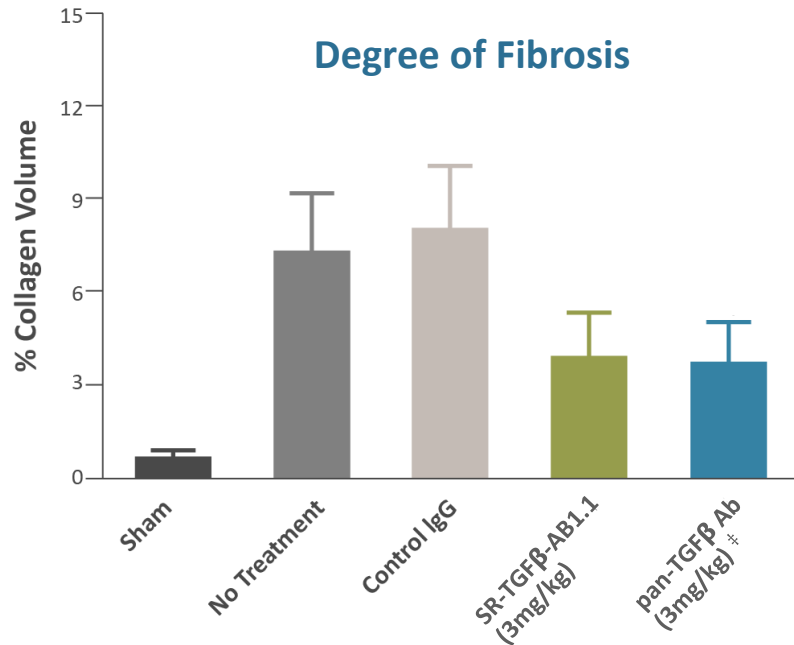
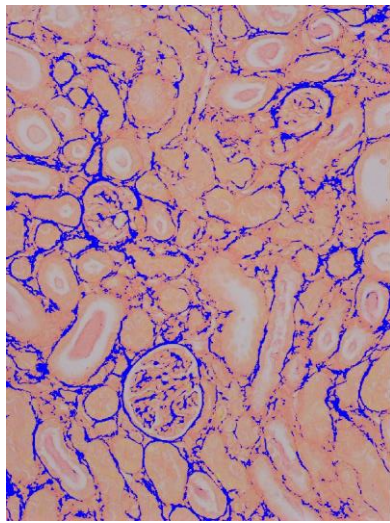
Inhibition of Latent TGF β 1 Activation Prevents Fibrosis

Acute Kidney Fibrosis Model (mouse UUO): Histomorphometry

Picrosirius red stain



Blue segmentation mask

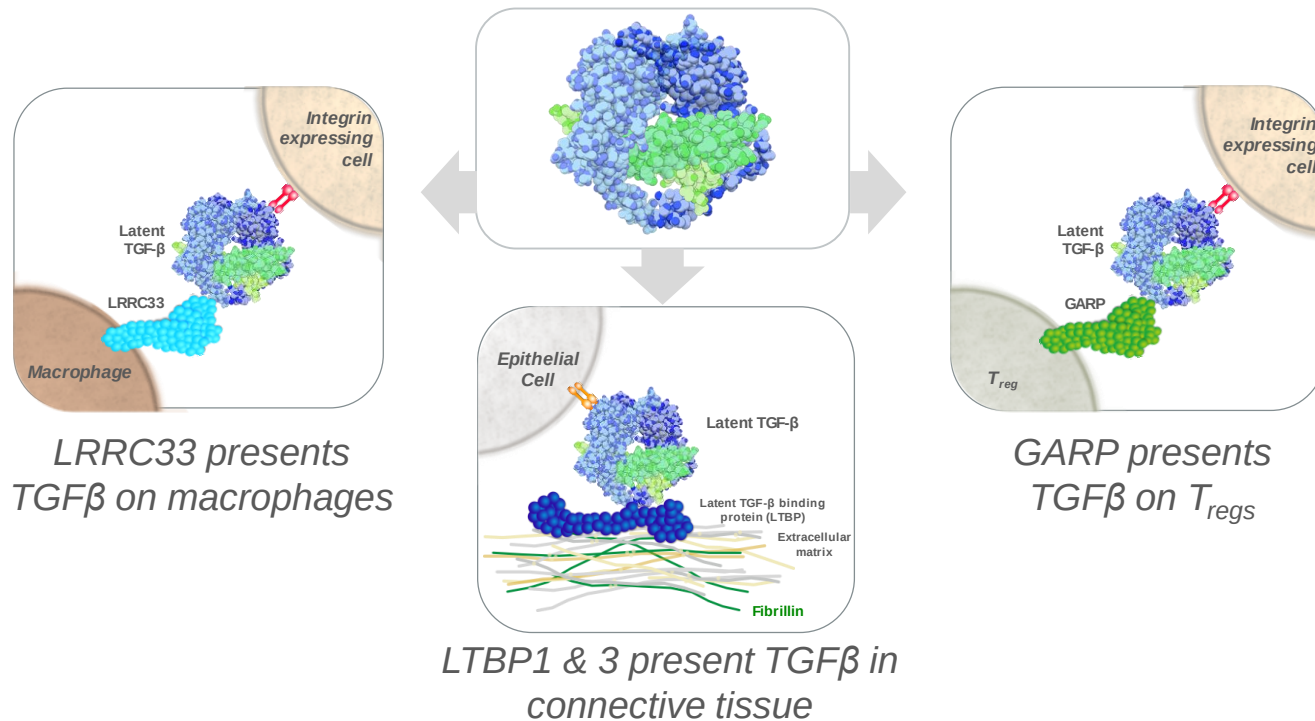


Recent Achievements and Upcoming Milestones

- ✓ Observed inhibition of TGFβ1 activation in vitro and immunomodulatory and anti-fibrotic activity in multiple in vivo disease models
- ✓ Completed 28-day pilot toxicology study of our leading antibody
 - ✓ Have not observed any drug-related toxicity
- ✓ Presented preclinical data at SITC demonstrating treatment with TGFβ1 inhibitor, SRTβ1-Ab3, and anti-PD1 leads to tumor regression or tumor control and significant survival benefit in syngeneic mouse models of primary resistance
- ❑ Actively evaluating our selective inhibitors of the activation of TGFβ1 in multiple disease models
- ❑ Nominate product candidate and lead indication by the end of 1H19
- ❑ Continue to advance active discovery programs for context-dependent inhibition of TGFβ1

Targeting Latent TGF β s Creates Multiple “Handles” For Selectivity

Context-Dependent Inhibition of TGF β 1



Recent Achievements

- ✓ Initiated Phase 1 clinical trial of SRK-015 in May 2018
- ✓ IND for SRK-015 in SMA was submitted to FDA in March and cleared in April 2018
- ✓ FDA granted Orphan Drug Designation for SRK-015 for the treatment of SMA
- ✓ EMA adopted positive opinion on Orphan Drug Designation for SRK-015 for the treatment of SMA
- ✓ Published preclinical data on the therapeutic benefits of inhibiting myostatin in mouse models of SMA in *Human Molecular Genetics*
- ✓ Issuance of U.S. Patent 9,758,576 covering myostatin activation inhibitors; exclusivity May 2034
- ✓ Raised \$86M in gross proceeds from IPO in May 2018

Upcoming Milestones

- ❑ Interim results from Phase 1 clinical trial of SRK-015 in healthy volunteers in 1Q19
- ❑ Initiate Phase 2 proof-of-concept study of SRK-015 in patients with SMA in 1Q19
- ❑ Identify next indication for SRK-015 in 1H19
- ❑ Nominate product candidate and lead indication in TGFβ1 program by the end of 1H19
- ❑ Initial functional results from Phase 2 proof-of-concept study of SRK-015 in patients with SMA in 2H19

Building for Success

