SCHOLAR ROCK

From New Insights to New Medicines

November 2018

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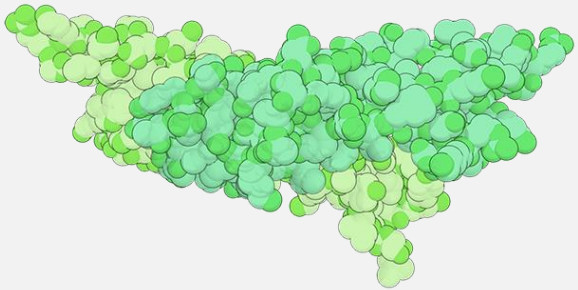
Nature's Growth Factor Activation Machinery

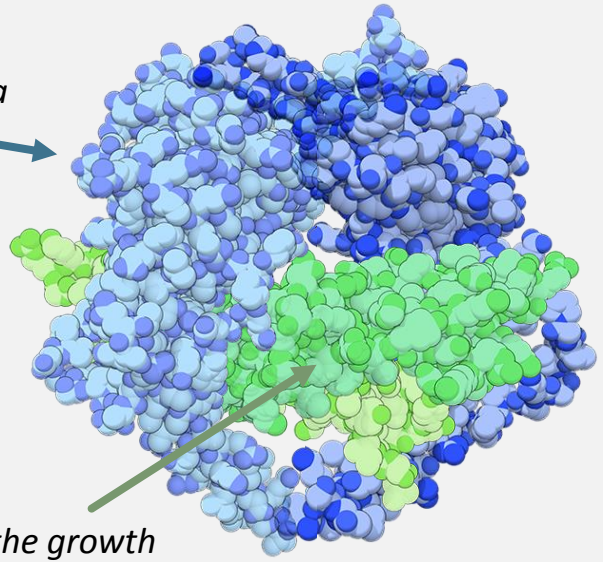
Mature TGFβ1

Active form of the growth factor



TGFβ1 Precursor Complex

TGFβ1 propeptide which forms a "cage"



Cage renders the growth factor inactive or "latent"

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

Shi, M., et al. Nature 474, 7351, 343-9 (2011)

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

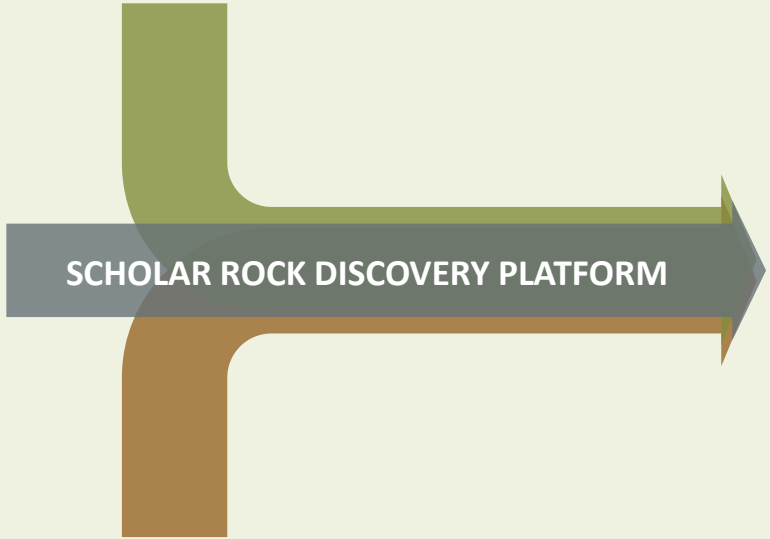
Localization of Effect

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



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						Scholar Rock	Phase 1 Trial Ongoing
Latent Myostatin	Additional Myostatin-Related Disorders						Scholar Rock	1H:2019 – Identify Next Indication
TGFβ1 Program								
Context-Independent								
Latent TGFβ1	Oncology/Immuno-oncology; Fibrosis						Scholar Rock	1H:2019 – Nominate Product Candidate
Context-Dependent								
Latent TGFβ1 / GARP	Oncology/Immuno-oncology						*Janssen Biotech, Inc.*	
Latent TGFβ1 / GARP & LRRC33	Oncology/Immuno-oncology						Scholar Rock	
Latent TGFβ1 / LRRC33	Oncology/Immuno-oncology						Scholar Rock	
Latent TGFβ1 / LTBP1 & LTBP3	Fibrosis						Scholar Rock	
BMP6 Program								
BMP6 Signaling Pathway	Anemia						Scholar Rock	

SRK-015: Inhibitor of Myostatin Activation

Potential First Muscle-Directed Therapy for SMA

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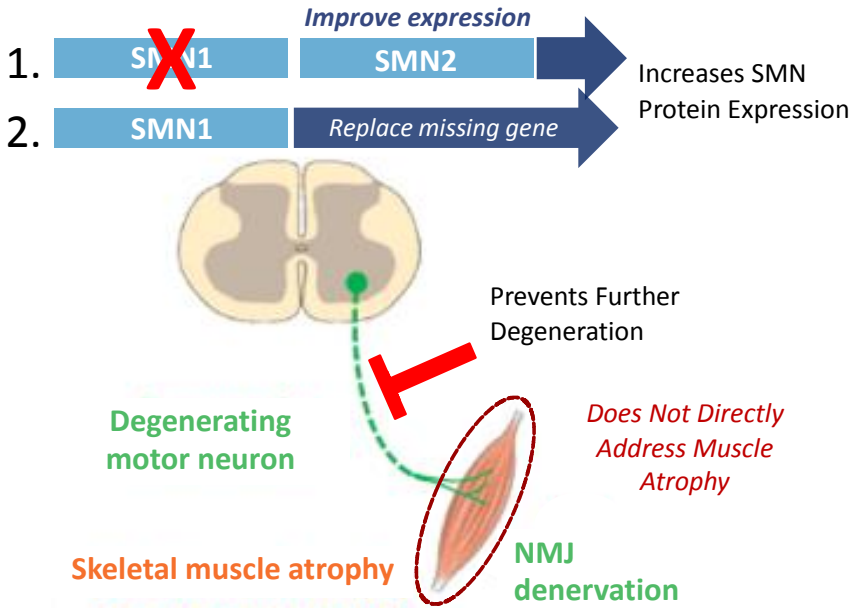
SMN Upregulators Do Not Directly Address Muscle Atrophy

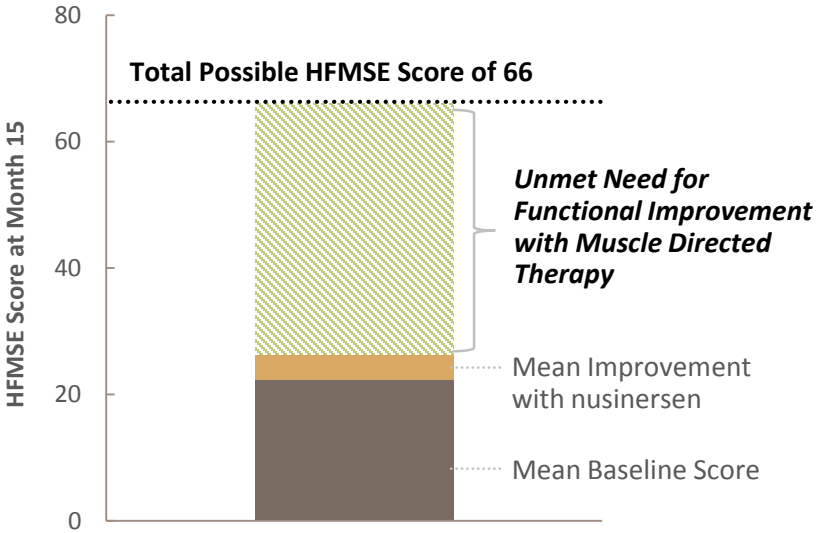
Significant Unmet Need Remains Despite Current Therapeutic Strategies



Adapted from images that were courtesy of the SMA Foundation

Muscle Function in SMA (Human)

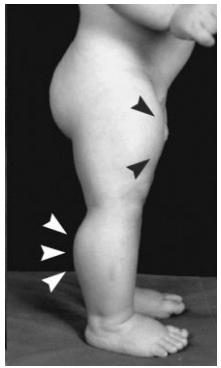
Hammersmith Functional Motor Scale Expanded (HFMSE)



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

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

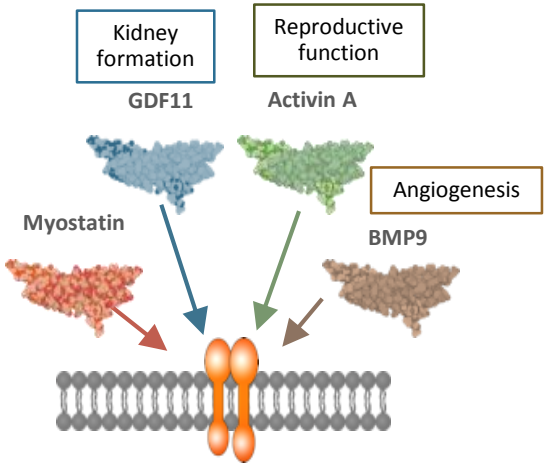
SRK-015: Aligning Therapeutic Approach with Myostatin Biology

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

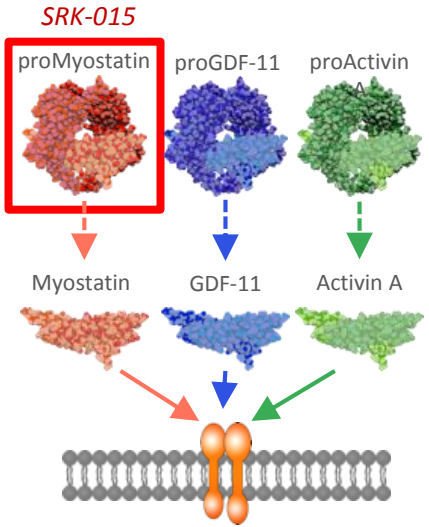
Traditional Approaches Lack Selectivity

- 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



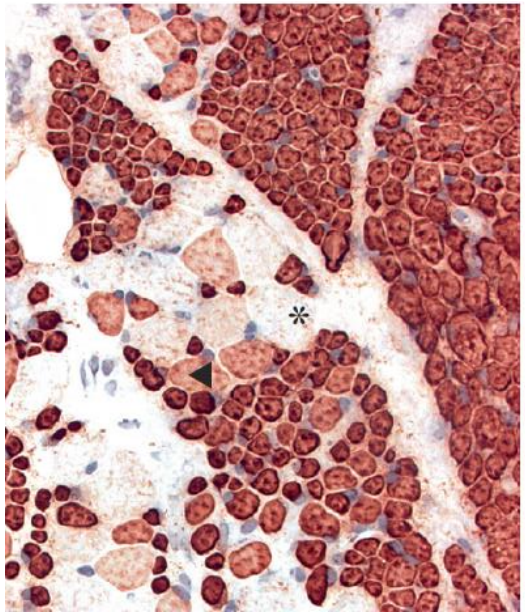
Scholar Rock Approach

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

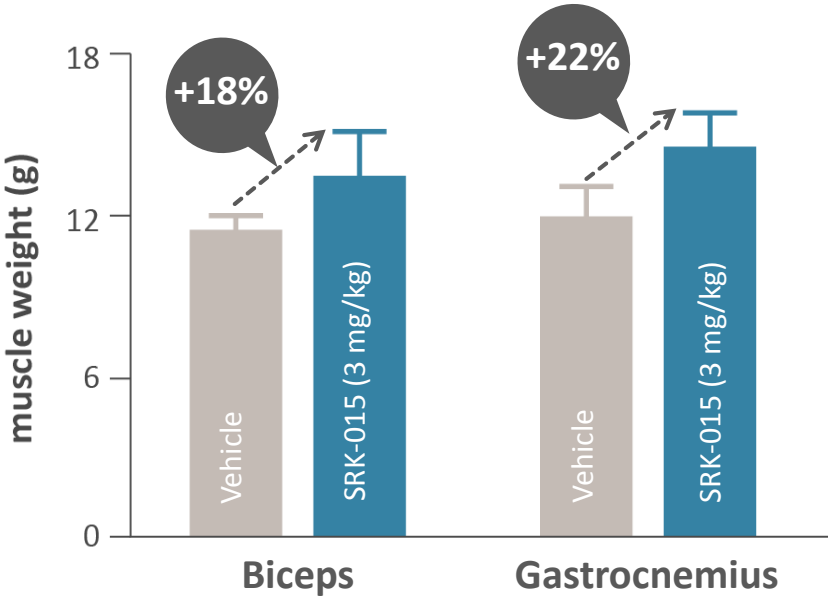


- Muscle is comprised of both slow-twitch and fast-twitch fibers
- Fast-twitch fibers significantly atrophy in patients with SMA

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

Healthy Non-Human Primate (Cyno)

Pronounced Effect on Fast-Twitch Muscle

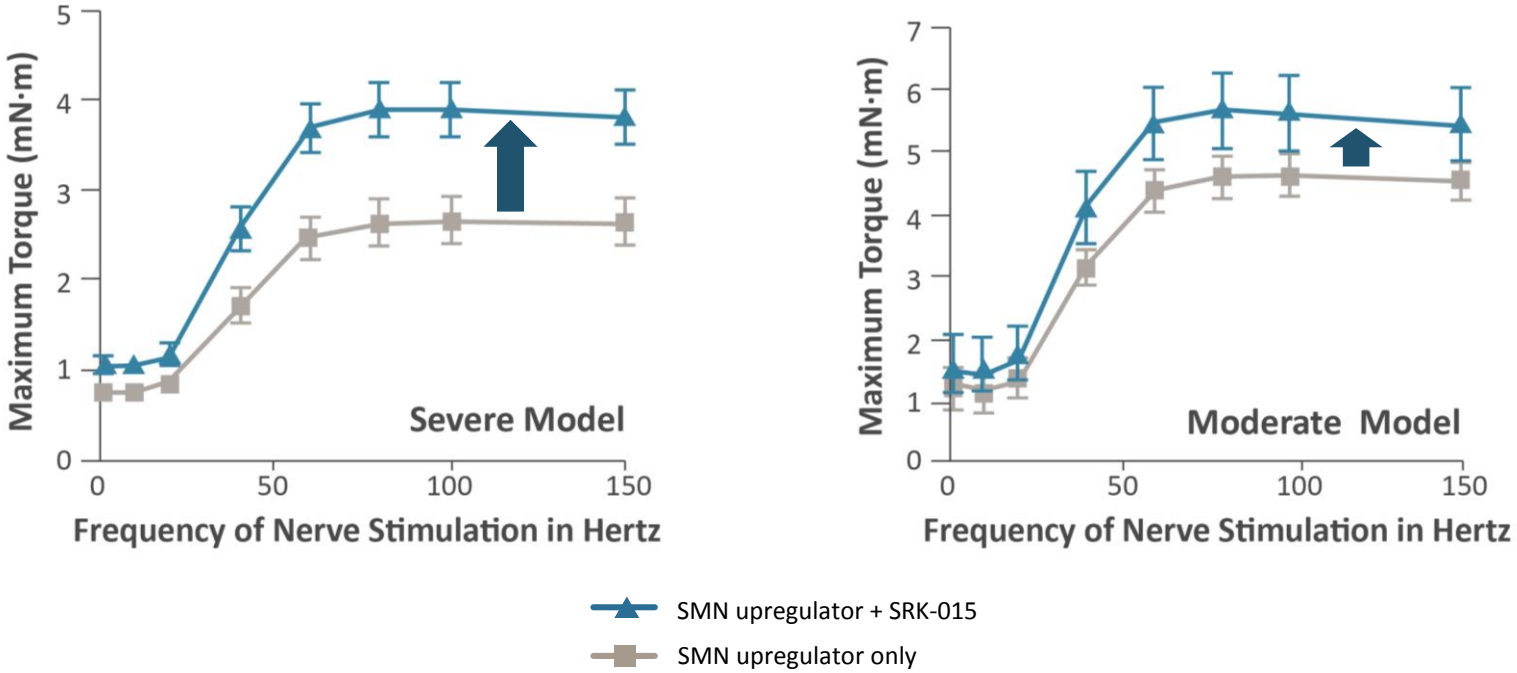


Six cynomolgus animals per group were treated once weekly with vehicle control or SRK-015 for 8 weeks and assessed after an additional 5 weeks

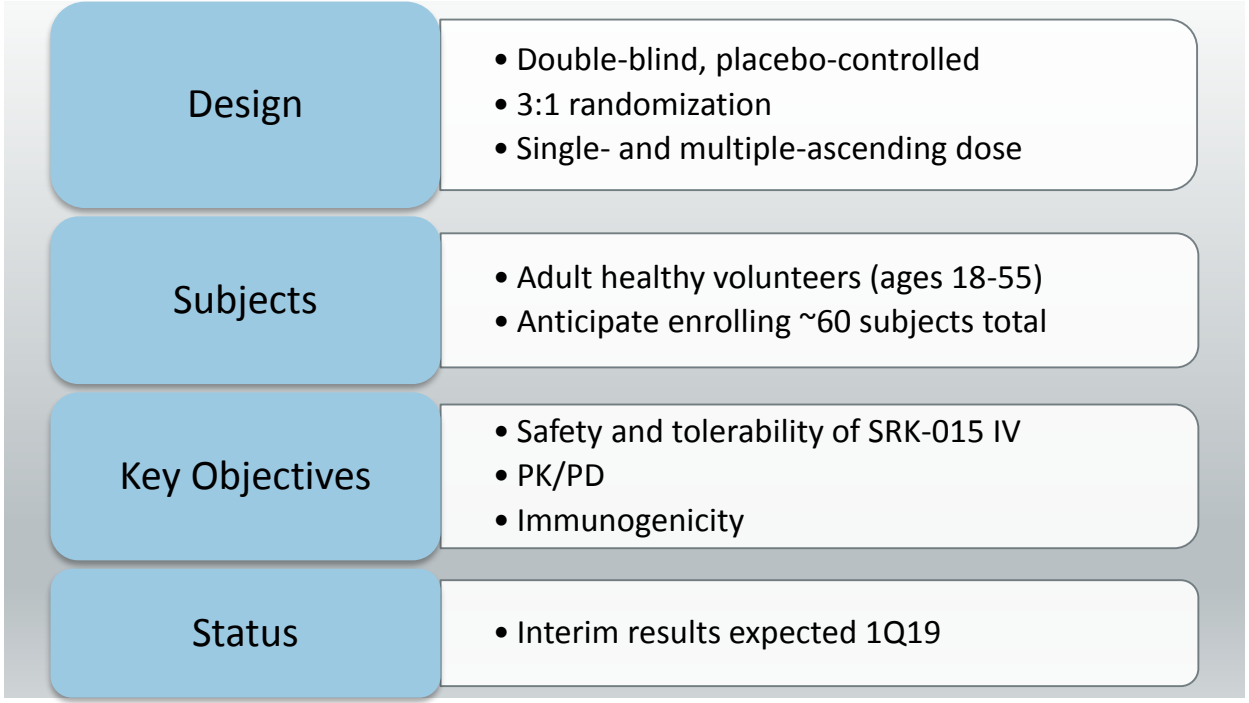
SRK-015 Demonstrates Potential Benefits Across SMA Severities

Genetic Model of SMA ("Δ7 Mouse") Demonstrate Improved *In Vivo* Muscle Force Generation

Strength of Plantarflexor Muscle Group



SRK-015 Phase 1 Trial Design

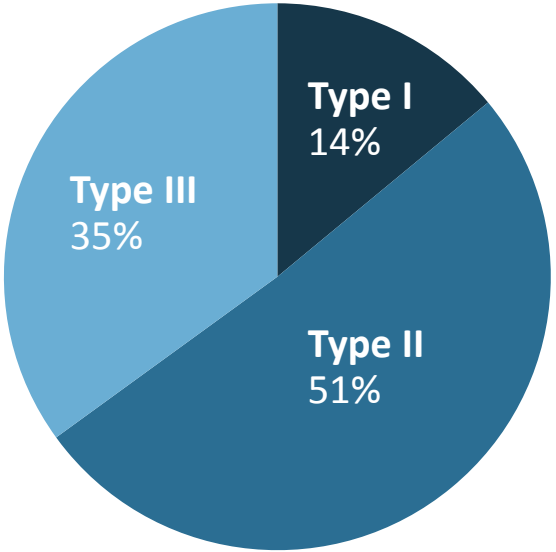


Initiate Phase 2 POC study in SMA in 1Q19

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

Lally et al, Orphanet Journal of Rare Diseases, 2017

Recent Achievements and Upcoming Milestones

- ✓ Orphan Drug Designation granted by FDA
- ✓ Completed IND-enabling toxicology studies
- ✓ IND in SMA submitted to FDA in March and cleared in April 2018
- ✓ Initiated Phase 1 clinical trial in healthy volunteers in May 2018
  - ✓ Advanced to multiple-ascending dose portion of trial
- ❑ Interim results from Phase 1 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

TGFβ1: Significant Opportunities in Oncology/Immuno-oncology and Fibrosis

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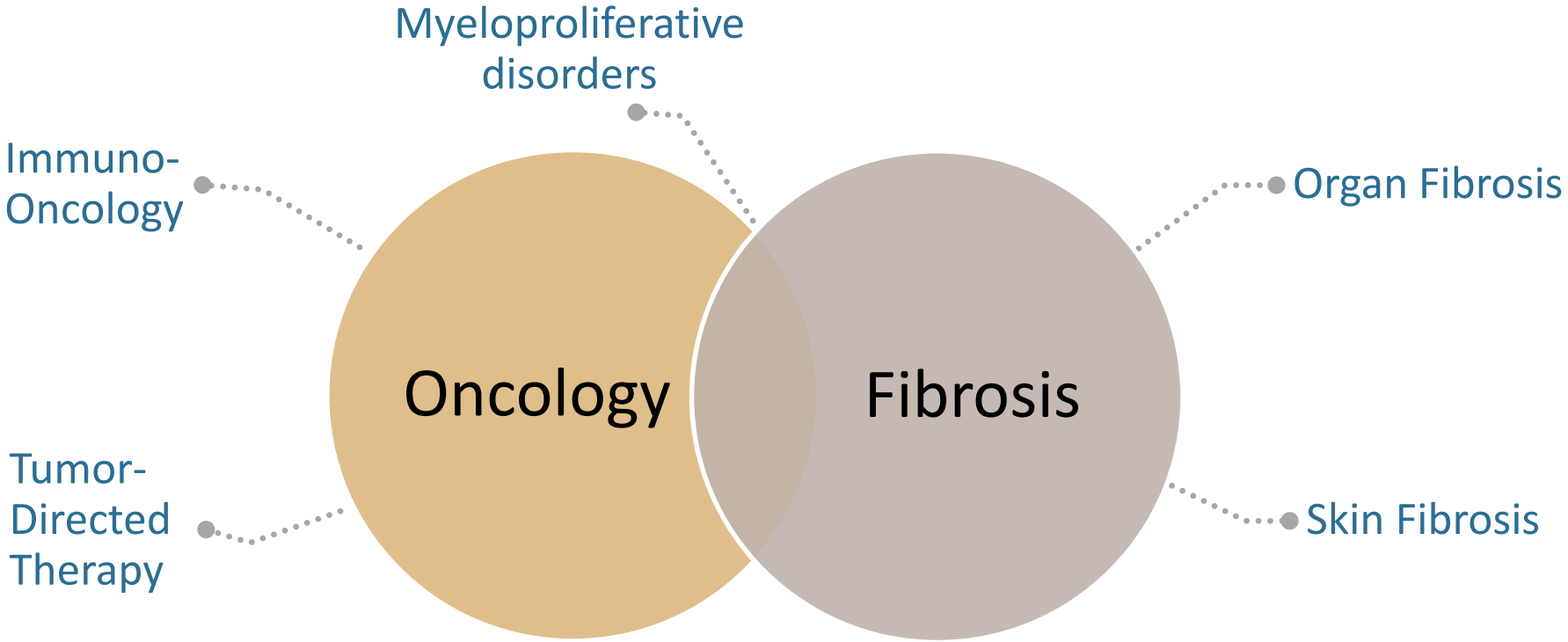
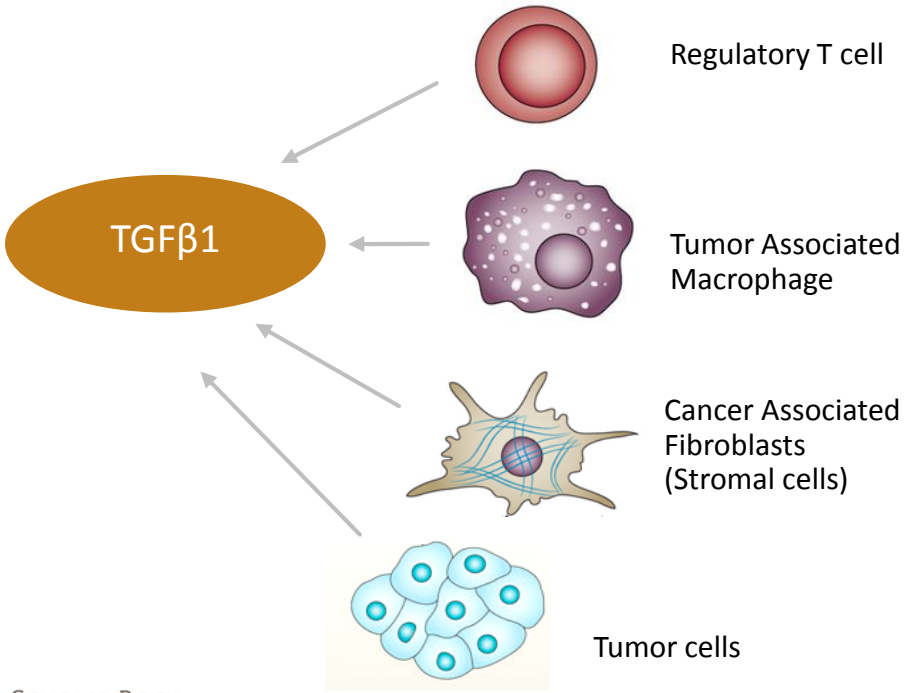
TGFβ1 Plays Central Role in Multiple Diseases with Unmet Need



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

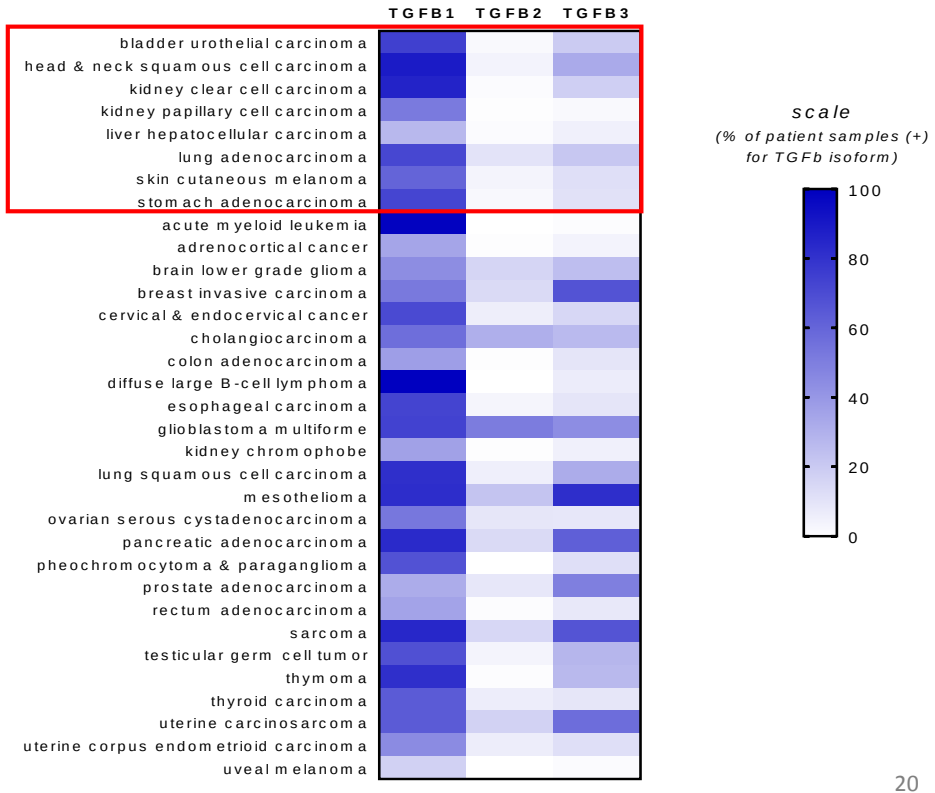
Sanjeev Mariathasan[1]*, Shannon J. Turley[1]*, Dorothee Nickles[1]*, Alessandra Castiglioni[1], Kobe Yuen[1], Yulei Wang[1], Edward E. Kadel III[1], Hartmut Koeppen[1], Jillian L. Astarita[1], Rafael Cubas[1], Suchit Jhunjhunwala[1], Romain Banchereau[1], Yagai Yang[1], Yinghui Guan[1], Cecile Chalouni[1], James Ziai[1], Yasin Şenbabaoğlu[1], Stephen Santoro[1], Daniel Sheinson[1], Jeffrey Hung[1], Jennifer M. Giltnane[1], Andrew A. Pierce[1], Kathryn Mesh[1], Steve Lianoglou[1], Johannes Riegler[1], Richard A. D. Carano[1], Pontus Eriksson[2], Mattias Höglund[2], Loan Somarriba[3], Daniel L. Halligan[3], Michiel S. van der Heijden[4], Yohann Loriot[5], Jonathan E. Rosenberg[6], Lawrence Fong[7], Ira Mellman[1], Daniel S. Chen[1], Marjorie Green[1], Christina Derleth[1], Gregg D. Fine[1], Priti S. Hegde[1], Richard Bourgon[1] & Thomas Powles[8]

- 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

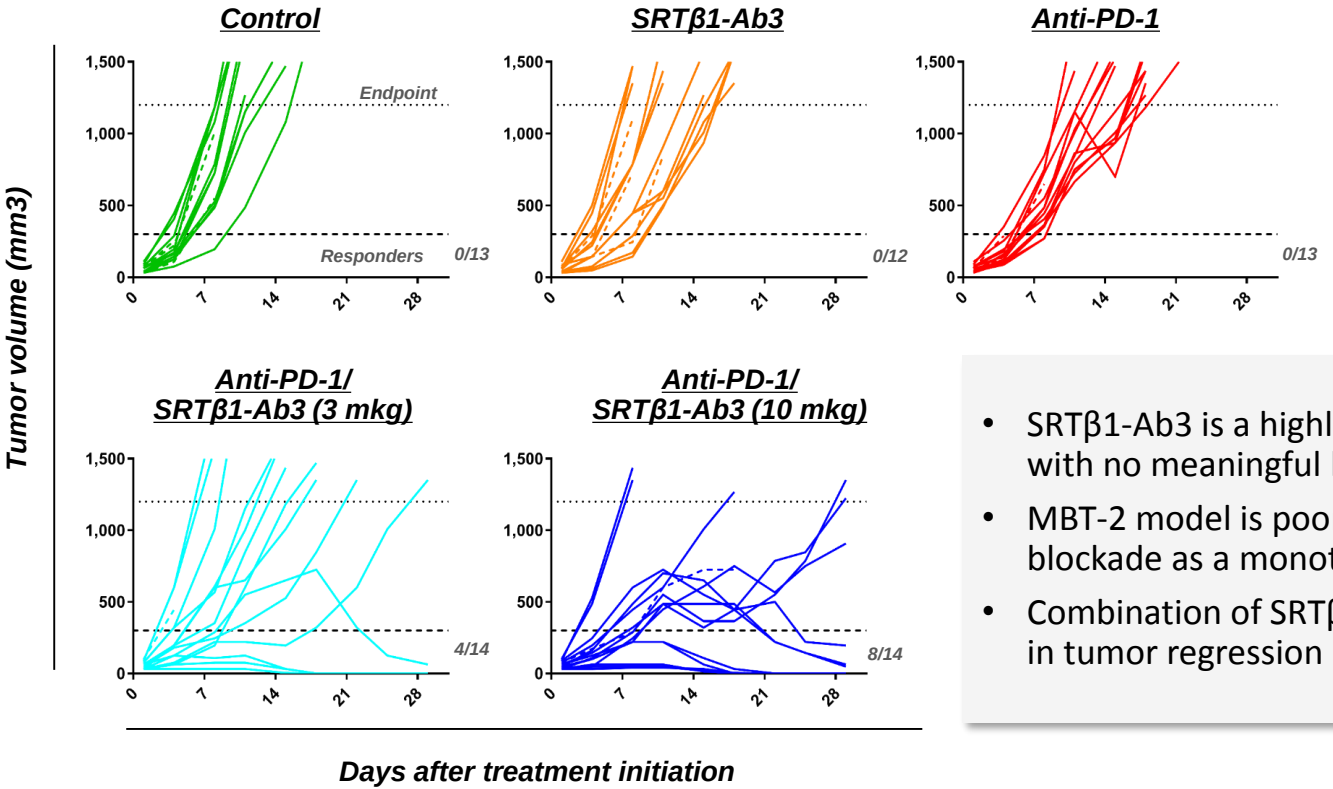
TGFβ1 is the Predominant Isoform in Most Human Tumors

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



TGFβ1 Blockade with SRTβ1-Ab3 Renders MBT-2 Tumors Susceptible to Anti-PD1 Therapy

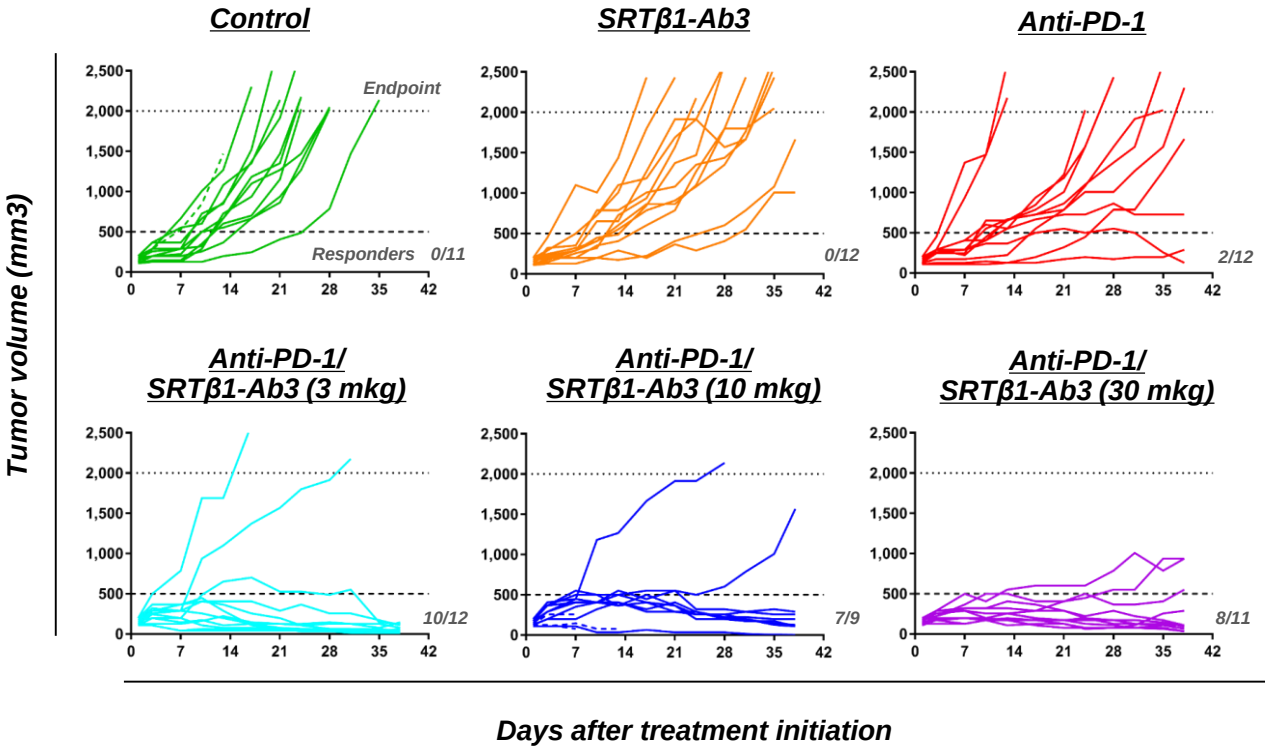


Dosing initiated when tumors reached 30-80 mm^3

Treatment with RMP1-14 anti-PD1 (5mg/kg twice weekly) and/or SRTβ1-Ab3 (once weekly at indicated dose)

- SRTβ1-Ab3 is a highly specific inhibitor of TGFβ1 with no meaningful binding to TGFβ2/TGFβ3
- MBT-2 model is poorly responsive to PD-1 blockade as a monotherapy
- Combination of SRTβ1-Ab3 and anti-PD1 resulted in tumor regression or tumor control

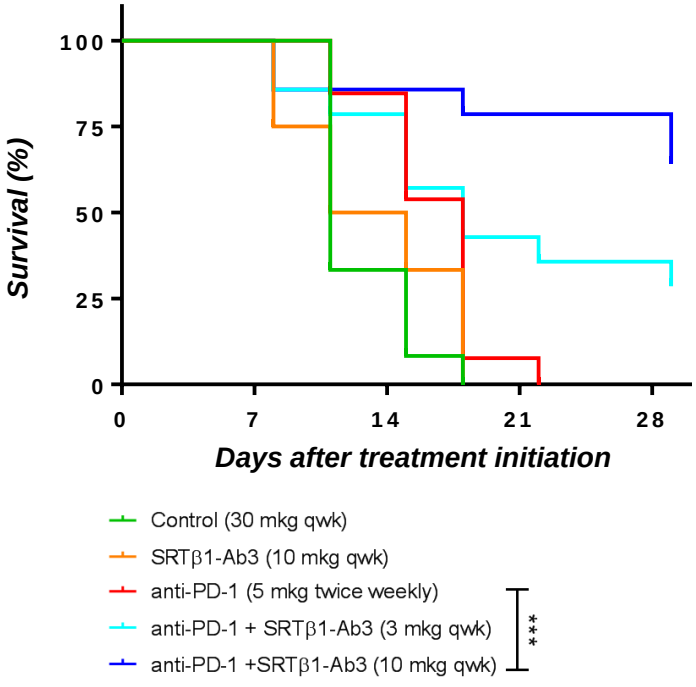
Anti-TGFβ1 Combination with PD-1 blockade is Effective in Cloudman S91 Melanoma Model



- Cloudman S91 model is poorly responsive to PD-1 blockade as a monotherapy
- Combination of SRTβ1-Ab3 and anti-PD1 resulted in tumor regression or tumor control
- Study ongoing

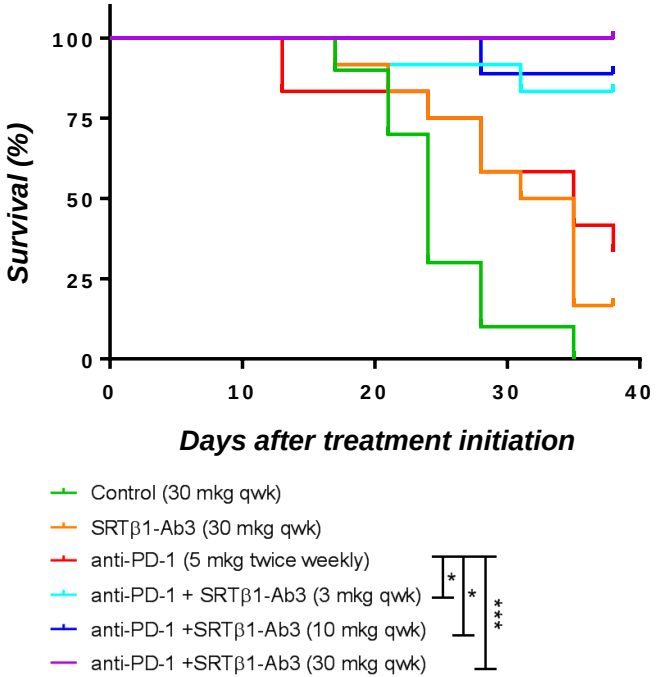
SRTβ1-Ab3 Combined with Anti-PD1 Therapy Leads to Significant Survival Benefit

MBT-2 Bladder Cancer Tumor Model



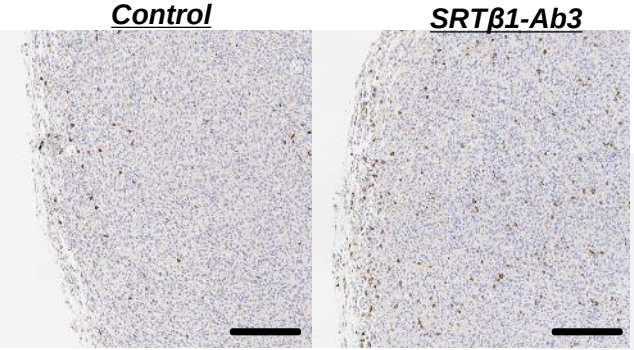
*** P<0.001 Log-rank (Mantel-Cox) test

Cloudman S91 Melanoma Tumor Model (study ongoing)



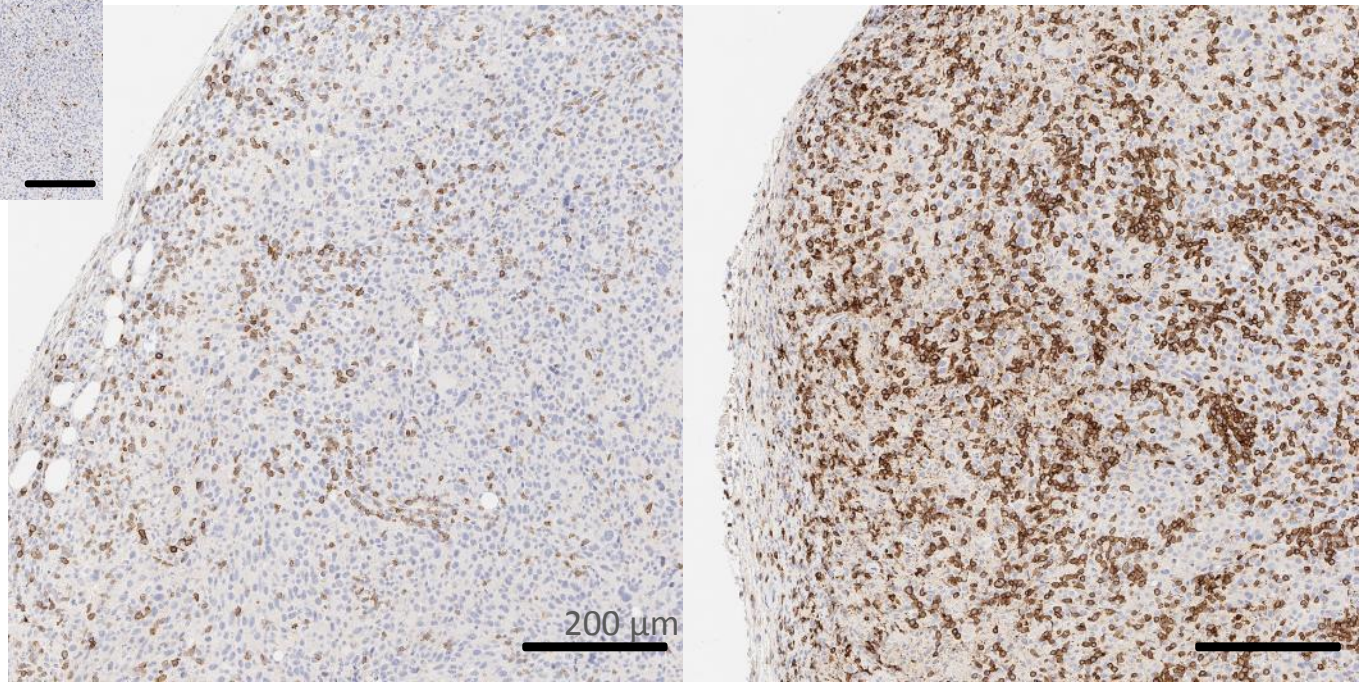
* P<0.05 Log-rank (Mantel-Cox) test
*** P<0.001

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



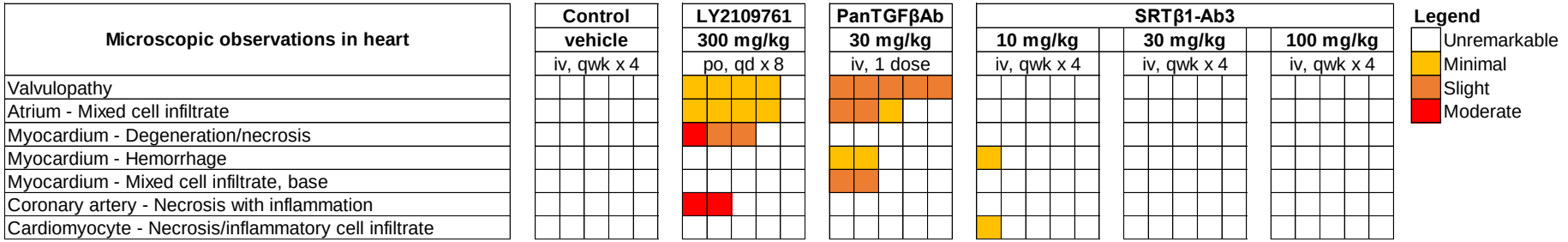
IHC of MBT-2 tumors at day 10

- 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

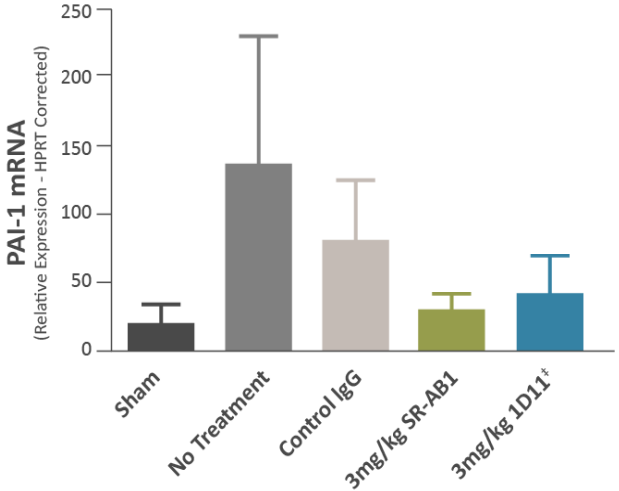


- Animals dosed with pan-TGFβ inhibitors, LY2109761 (inhibitor of ALK5, common TGFβ receptor kinase) or pan-TGFβ antibody, exhibited expected cardiac findings based on published data
- Exposure as assessed by SRTβ1-Ab3 serum concentration reached 2,300 µg/ml following 4 weekly doses of 100 mg/kg
- No 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) is >100 mg/kg per week

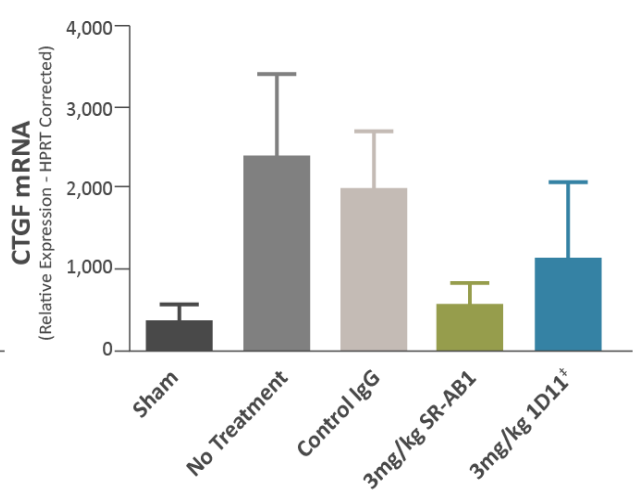
TGFβ is a Central Driver of Fibrotic Disease

Acute Kidney Fibrosis Model (mouse UUO): Gene Expression

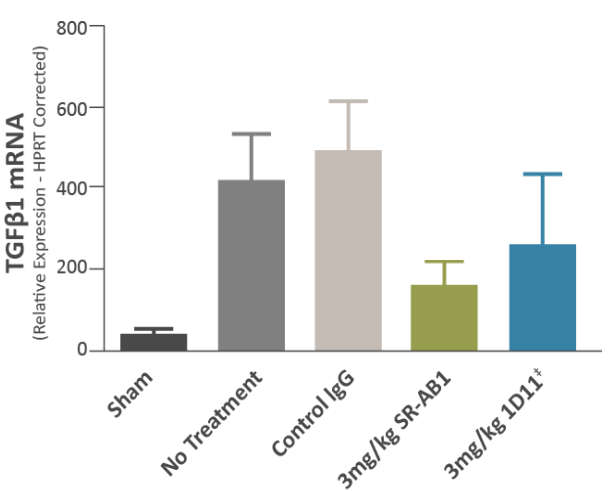
PAI-1
(Plasminogen Activator Inhibitor 1)



CTGF
(Connective Tissue Growth Factor)



TGFβ1
(Transforming Growth Factor beta 1)

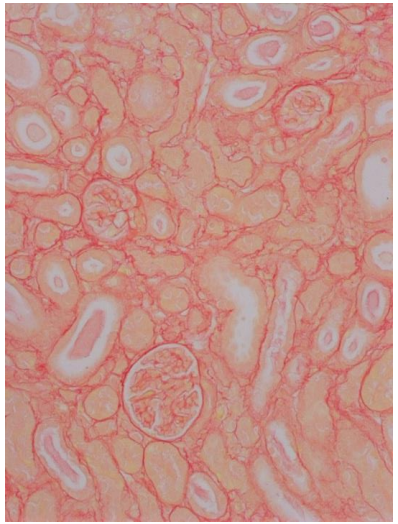


‡1D11 is an inhibitor of all three isoforms of mature TGFβ

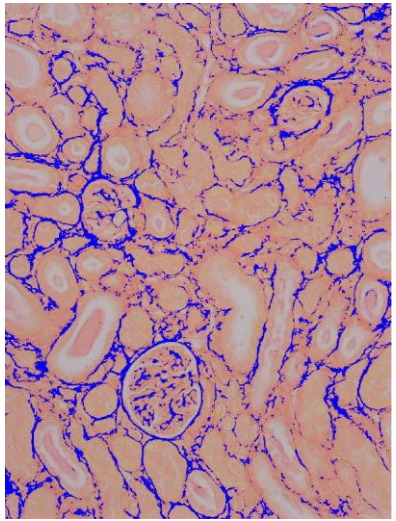
Inhibition of Latent TGFβ1 Activation Prevents Fibrosis

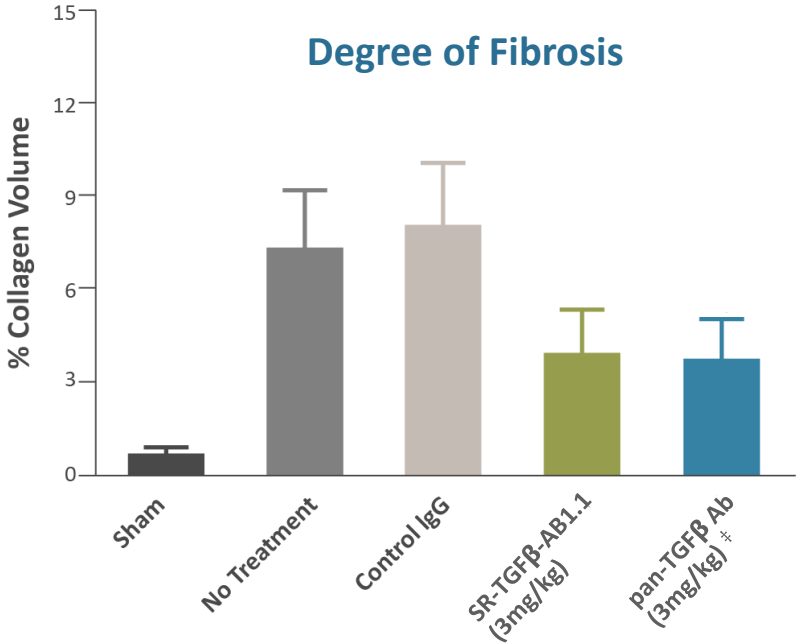
Acute Kidney Fibrosis Model (mouse UUO): Histomorphometry

Picrosirius red stain



Blue segmentation mask





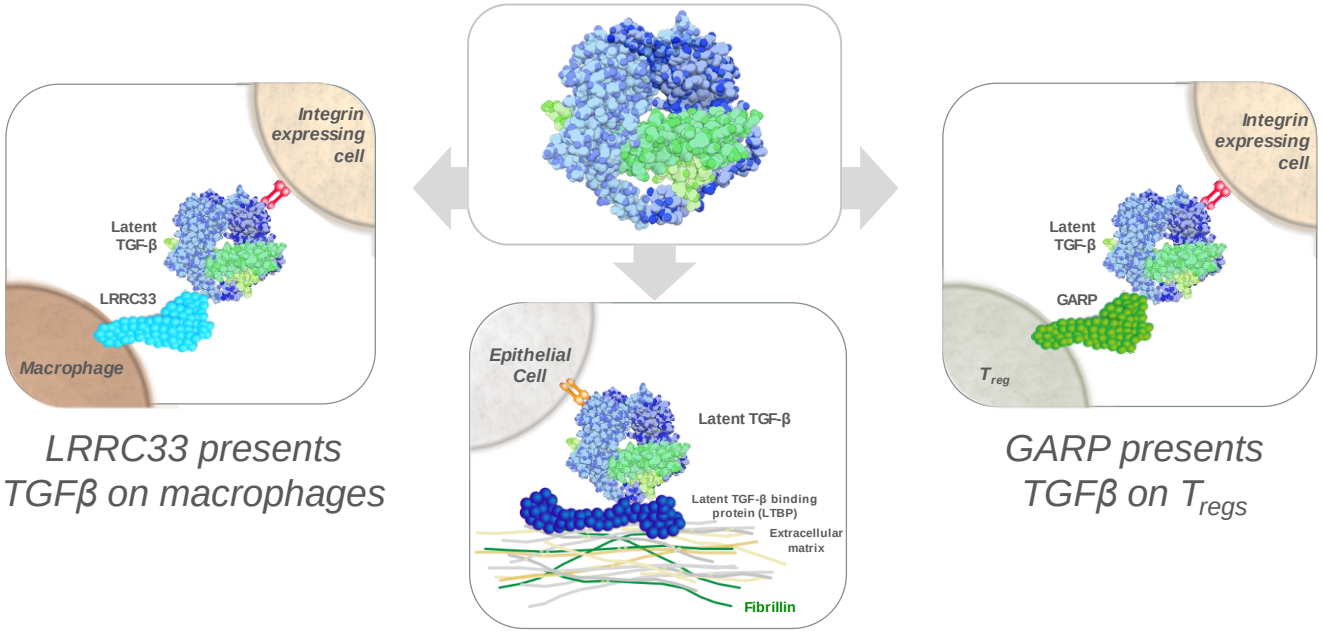
‡1D11 is an inhibitor of all three isoforms of mature TGFβ

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 TGFβs Creates Multiple "Handles" For Selectivity

Context-Dependent Inhibition of TGFβ1



LRRC33 presents TGFβ on macrophages

LTBP1 & 3 present TGFβ in connective tissue

GARP presents TGFβ on T_{regs}

Recent Achievements

- ✓ Initiated Phase 1 clinical trial of SRK-015 in May 2018
  - ✓ Completed enrollment in multiple-ascending dose portion of trial
- ✓ 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
- ✓ 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 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