



SCHOLAR ROCK

From New Insights to New Medicines

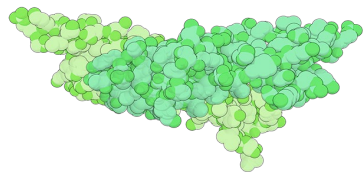
November 2019

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Novel Approach to Selective Modulation of Growth Factor Signaling

Traditional approaches inhibit growth factors **after** activation



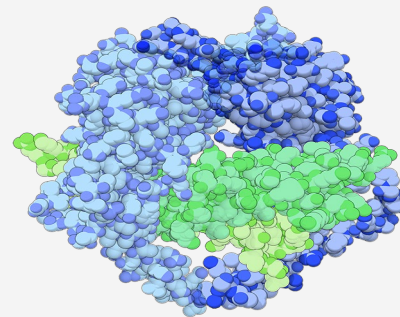
Traditional Target

"Mature" Growth Factor

...but have been limited by:

- Structural similarities
- Overlapping sets of related receptors
- Diverse and overlapping physiological roles

Scholar Rock's Target



Growth Factor Precursor (Latent Form)

- Inhibits **activation of growth factor precursors** to significantly improve:
 - Selectivity
 - Potency
 - Localization of effect
- Preclinical/clinical data demonstrate successful targeting of latent growth factors in disease settings
- Developing growing pipeline across neuromuscular disorders, oncology, fibrosis and anemia

Robust Pipeline Portfolio

Target / Program		Indication	Discovery / Early Preclinical	Preclinical	Phase 1	Phase 2	Rights / Partner	Next Anticipated Milestone
INTERNAL PROPRIETARY PROGRAMS								
Pro/Latent Myostatin	SRK-015	Spinal Muscular Atrophy (3 distinct Type 2 and Type 3 patient populations)						Interim Efficacy and Safety Results in 1H20
	SRK-015	Myostatin-Related Disorders						Identify Next Indication in 2020
Latent TGFβ	SRK-181 (Context-Independent Latent TGFβ1)	Immuno-oncology (Primary resistance to CBTs*)						Initiate Phase 1 Trial in Patients with Solid Tumors in 1Q20
	SRK-181 (Context-Independent Latent TGFβ1)	Oncology						
	Context-Dependent Latent TGFβ1 / Immune Cell	Oncology/Immuno-oncology						
RGMc	BMP6 Signaling Pathway (anti-RGMc)	Iron-Restricted Anemias						Nominate Product Candidate in 2020
PARTNERED PROGRAMS								
Latent TGFβ	Context-Independent Latent TGFβ1	Fibrosis						
	Context-Dependent Latent TGFβ1 / LTBP1 & LTBP3	Fibrosis						
	Undisclosed Program	Fibrosis						
	Context-Dependent Latent TGFβ1 / GARP	Oncology/Immuno-oncology					Janssen Biotech, Inc	

Upcoming Key R&D Milestones

Spinal Muscular Atrophy (SMA)

- ✓ Initiate SRK-015 Phase 2 proof-of-concept SMA trial by the end of 1Q19
- ✓ Commence patient dosing in SRK-015 Phase 2 SMA proof-of-concept trial in 2Q19
- ✓ Present final Phase 1 results at Cure SMA Annual Conference being held June 28-July 1, 2019
- Announce SRK-015 Phase 2 trial read-outs:
 - ✓ Preliminary PK/PD analysis by end of 2019
 - Interim efficacy and safety results in a subset of patients at 6 months in 1H20
 - Top-line results of 12-month treatment period 4Q20-1Q21

Oncology

- Initiate SRK-181 Phase 1 dose escalation and POC trial in patients with solid tumors in 1Q20
- Continue to advance active discovery programs for context-dependent inhibition of TGFβ1

Fibrosis

- Continue to conduct fibrosis discovery and preclinical studies in partnership with Gilead

Anemias

- Nominate product candidate in RGMc program in 2020

SRK-015: Inhibitor of Myostatin Activation

Potential First Muscle-Directed Therapy for SMA



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SRK-015: Highly Specific Inhibitor of Latent Myostatin



- Myostatin is a genetically-validated, negative regulator of muscle mass expressed in skeletal muscle tissue
- Vertebrates lacking the myostatin gene are healthy and display increased muscle mass and strength
- Preclinical and clinical data to date provide strong rationale for developing SRK-015 to improve muscle function in Spinal Muscular Atrophy (SMA)



Differentiated approach with SRK-015:

- *Fully human monoclonal antibody (mAb)*
- *Highly selective inhibitor of the activation of myostatin precursor*
- *Half-life of 23-33 days*
- *Orphan Drug Designation for SMA granted by FDA and EC*
- *US Patent 9,758,576 covers mAbs that inhibit the activation of the myostatin precursor (expiry in 2034)*

Significant Unmet Need Remains Despite Current Therapies

SMN Upregulator Therapies

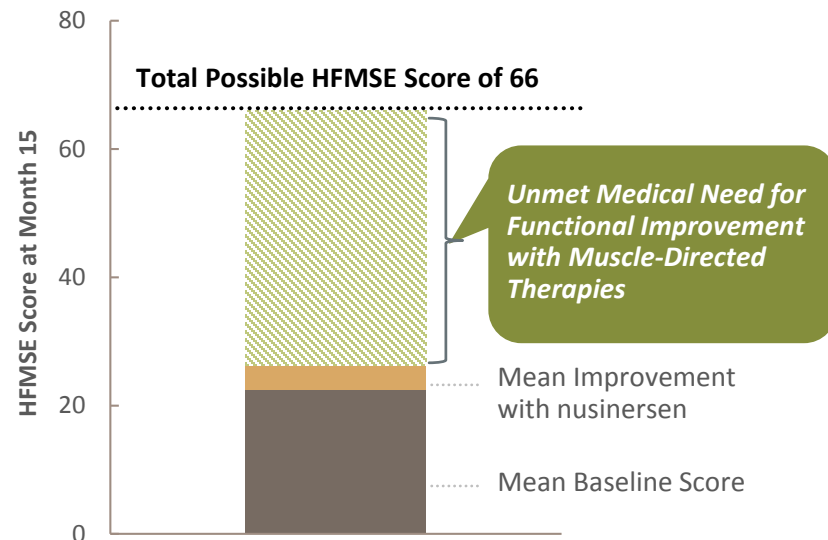
Address SMN deficiency to prevent further motor neuron deterioration

Muscle-Directed Therapies (SRK-015)

Act directly on muscle with aim to improve functional performance

SRK-015 has potential to drive functional performance across a range of severity observed in SMA

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

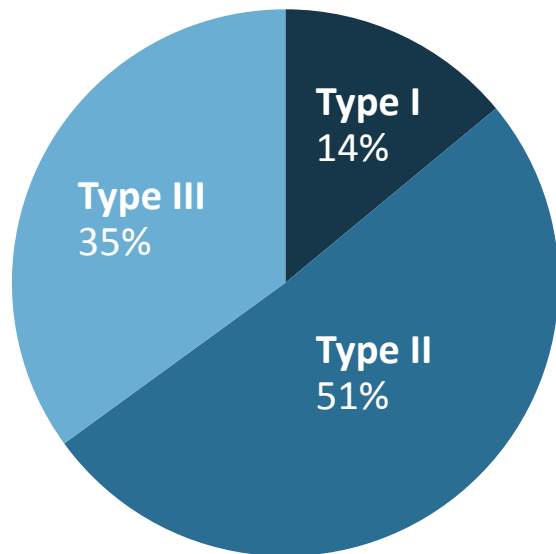


Mean improvement in HFMSE score experienced by patients with later-onset SMA in the Phase 3 CHERISH clinical trial of nusinersen

SRK-015 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

Ambulatory type III:

- Limited mobility and substantial morbidity

Type IV:

- Population not well-characterized

Focus of Phase 2 Trial

*Potential to use
SRK-015 in conjunction
with SMN upregulators*

*Potential to use SRK-015
as monotherapy or in
conjunction with SMN
upregulators*

SRK-015 Phase 2 Trial Design



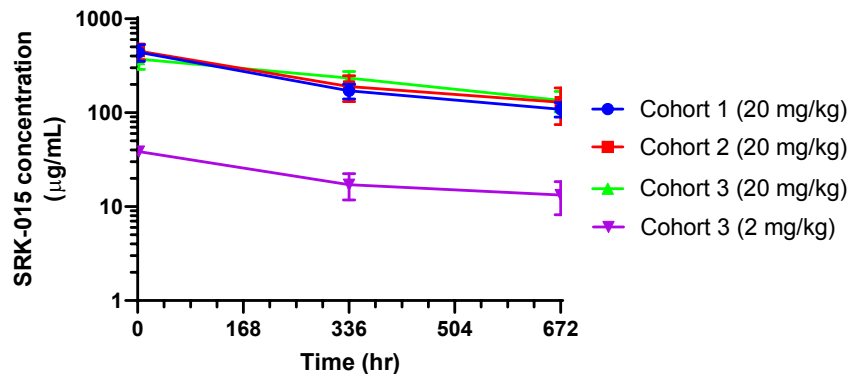
	Cohort 1	Cohort 2	Cohort 3
Design	• N= 20; ages 5-21 • Open-label, single-arm • 20 mg/kg SRK-015 IV Q4W • 12-month treatment period	• N= 15; ages 5-21 • Open-label, single-arm • 20 mg/kg SRK-015 IV Q4W • 12-month treatment period	• N= 20; ages ≥ 2 • Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg SRK-015 IV Q4W • 12-month treatment period
Subjects	• Ambulatory Type 3 SMA	• Type 2 or non-ambulatory Type 3 SMA • Receiving treatment with approved SMN upregulator	• Type 2 SMA • Initiated treatment with approved SMN upregulator before age 5
Primary Objectives	• Safety • Mean change from baseline in RHS	• Safety • Mean change from baseline in HFMSE	• Safety • Mean change from baseline in HFMSE

Preliminary PK Data Shows SRK-015 Exposure in Patients with SMA Consistent with that in Healthy Volunteers

SRK-015 Displayed Well-Behaved, Linear PK Profile

- Minimal variability across TOPAZ cohorts
- Preliminary PK observations consistent with Phase 1 trial results in healthy volunteers
- Dose proportional increase in serum drug exposure between low (2 mg/kg) and high (20 mg/kg) doses

Preliminary TOPAZ Phase 2 Pharmacokinetic (PK) Data

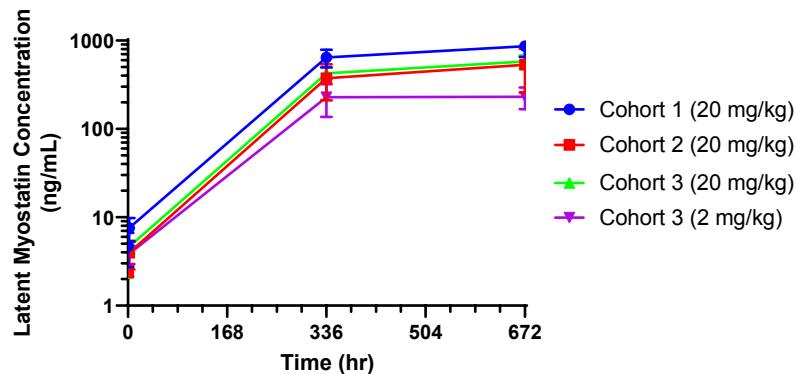


Preliminary Biomarker Data Provide First Demonstration of Target Engagement in Patients with SMA

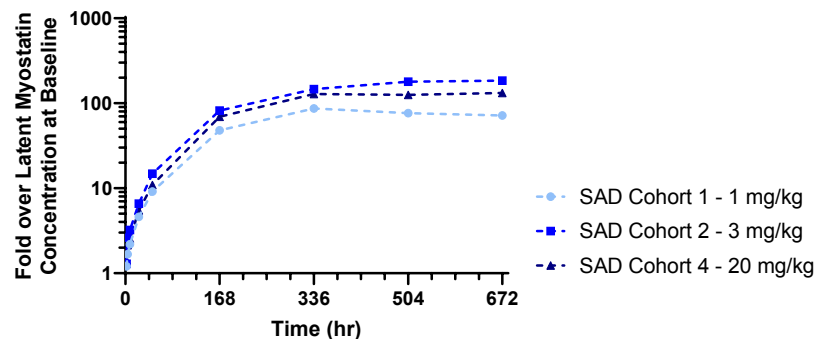
Robust Target Engagement Observed in TOPAZ

- ~100-fold increases in serum latent myostatin levels following a single 20 mg/kg dose in all cohorts
- Increases in latent myostatin were dose-dependent
- Confirms presence of latent myostatin in patients with SMA
- Fold increase from baseline in first 4 weeks after SRK-015 dose were comparable between SMA patients in TOPAZ and healthy volunteers in Phase 1

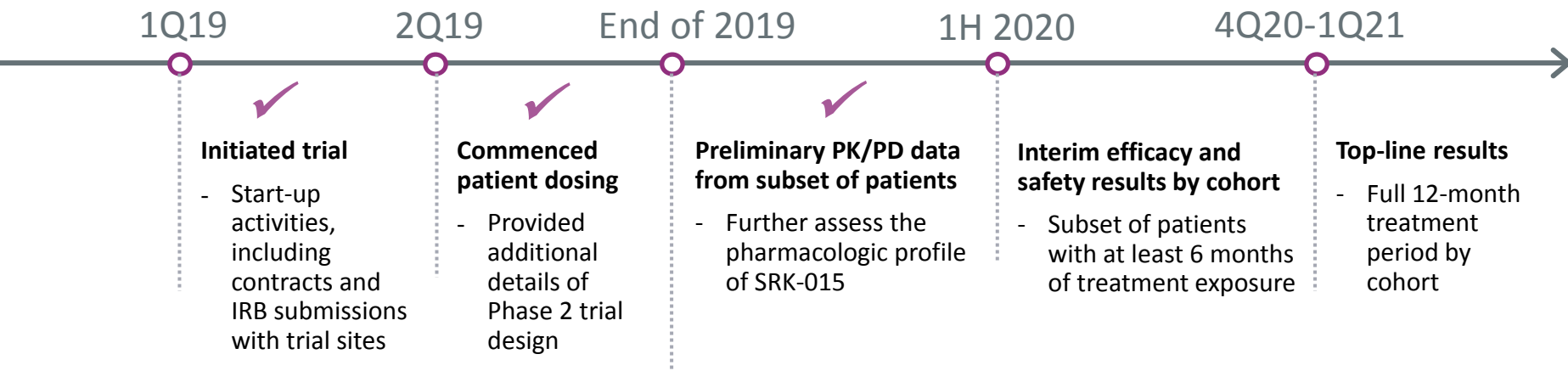
Latent Myostatin Change over Baseline in TOPAZ Trial



Latent Myostatin Change over Baseline in Phase 1 HV Trial



SRK-015: Path to Top-Line Results in TOPAZ SMA Trial



SRK-015 has the potential to be the first muscle-directed therapy for patients with SMA

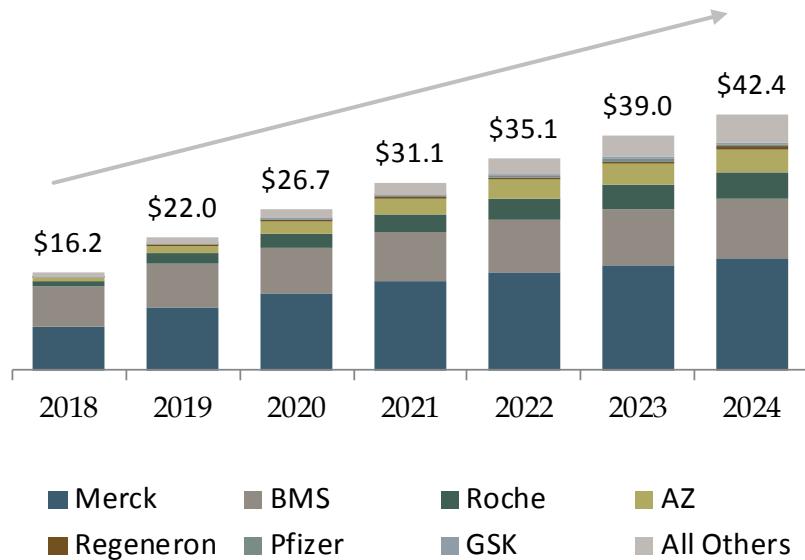
TGF β 1: Significant Opportunities in Oncology/Immuno-oncology



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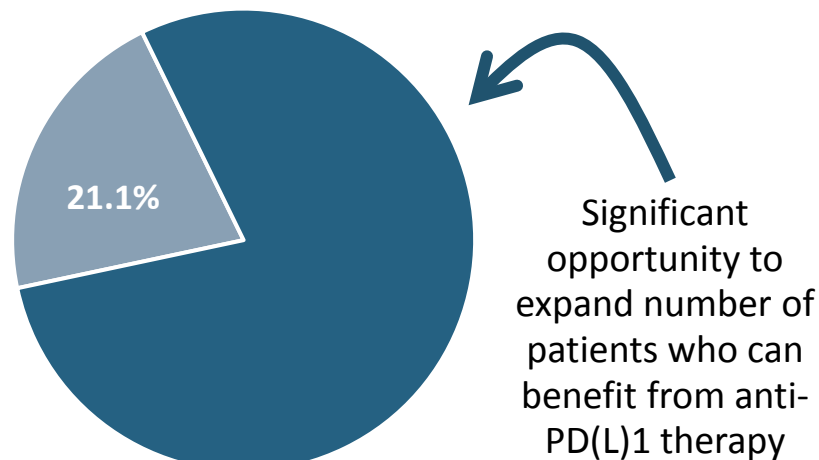
Anti-PD(L)1 Becoming Backbone Therapy Across Oncology; Significant Unmet Need Remains

Checkpoint Market Expected to Nearly Triple Over Next Few Years...



Source: Company information, Wall Street research, Evaluate Pharma

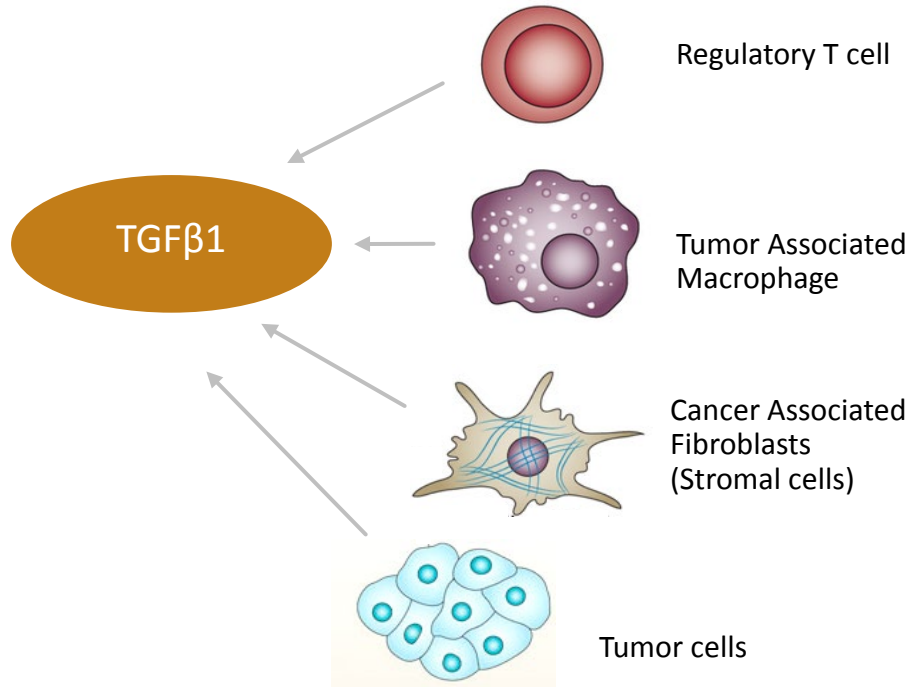
Yet only 21% of patients show complete or partial response to anti-PD(L)1 therapy



Source: Carretero-Gonzalez et al. (2018) Oncotarget 9:8706-8715
Meta-analysis of twelve randomized trials with control arm or adequate safety profile (includes nivolumab, pembrolizumab, and atezolizumab)

Inhibition of TGF β 1: Multipronged Approach for Immuno-Oncology

TGF β 1 is a key driver of immune system evasion by cancer cells



- Pathway analysis in patient tumors points to TGF β 1 as major determinant of primary resistance to anti-PD(L)1
- TGF β 1 creates 'immune excluded' tumor microenvironment

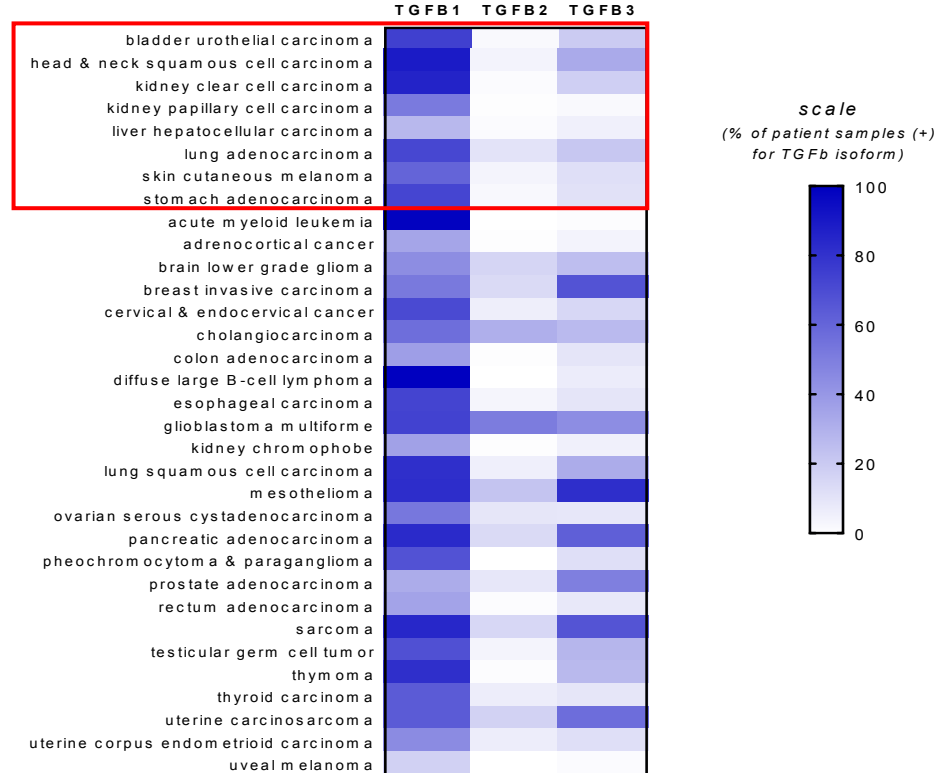
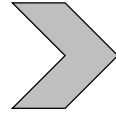


Selective inhibition of TGF β 1 activation has the potential to significantly increase anti-PD(L)1 response rates

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



SRK-181 has Potential to Meaningfully Expand Number of Patients Who Could Benefit from Checkpoint Inhibitors

Differentiated approach with SRK-181

- *Highly selective inhibitor of the activation of latent TGFβ1*
- *Minimal or no binding to latent TGFβ2 and TGFβ3 isoforms*
- *Fully human mAb*



**1Q20: Initiate Phase 1 trial
in patients with locally
advanced or metastatic
solid tumors**

Preclinical models show potential of SRK-181 in overcoming primary resistance to checkpoints

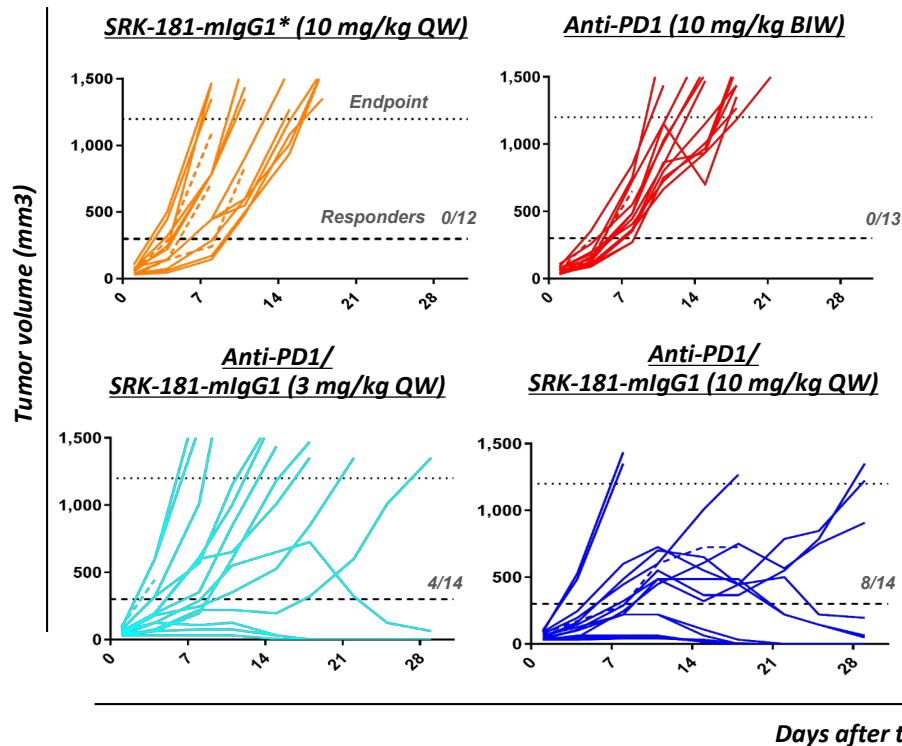
Treatment with SRK-181-mIgG1*:

- Rendered resistant TGFβ1- and TGFβ1/TGFβ3 co-expressing tumor models sensitive to anti-PD1
- Led to tumor regression and survival benefit when combined with anti-PD1
- Enabled infiltration and expansion of CD8+ T cells when combined with anti-PD1
- Avoided cardio toxicity associated with traditional less selective approaches

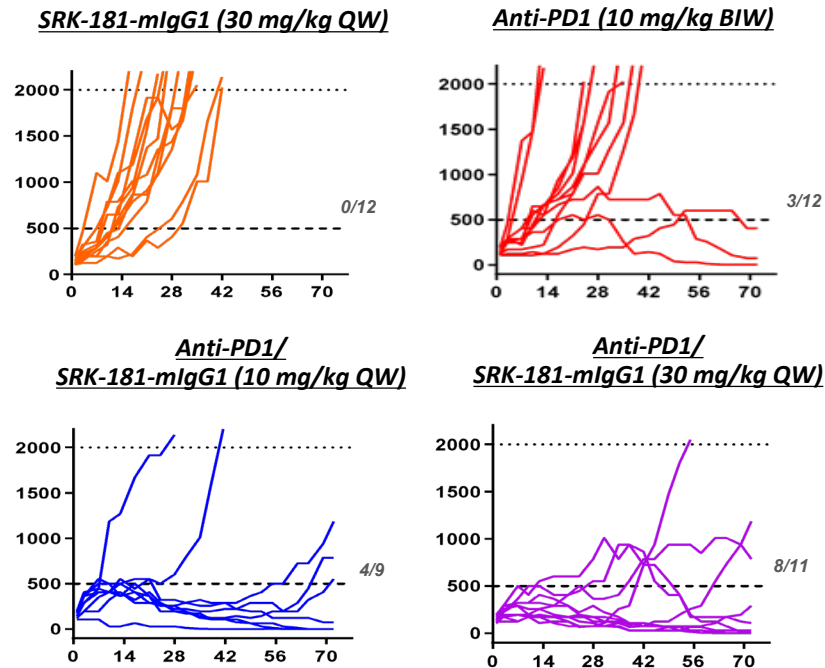
Syngeneic mouse tumor models specifically selected to reflect human tumor biology

TGF β 1 Blockade with SRK-181-mlgG1 Rendered Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

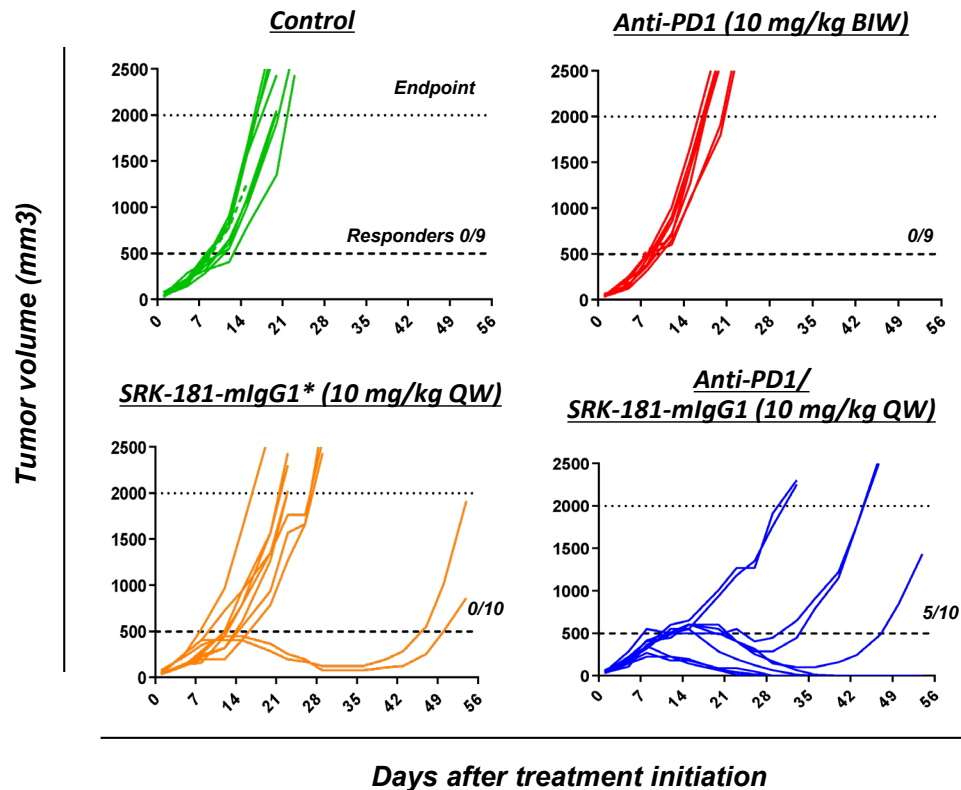
Bladder Cancer



Melanoma



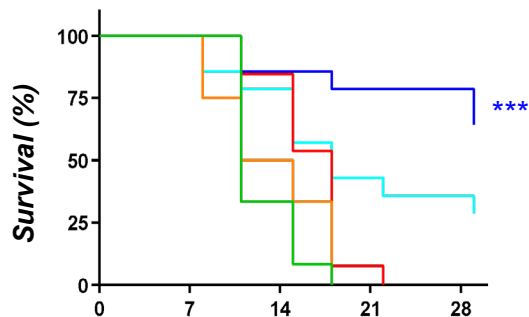
Inhibiting TGF β 1 Alone Was Sufficient to Sensitize Preclinical TGF β 1/3-Expressing Breast Cancer Model



- EMT6 model expresses both TGF β 1 and TGF β 3
- Model is poorly responsive to PD1 blockade as a monotherapy
- Combination of SRK-181-mIgG1 and anti-PD1 resulted in tumor regression or tumor control

SRK-181-mIgG1[†] Combined with Anti-PD1 Therapy Led to Significant Survival Benefit in Preclinical Tumor Models

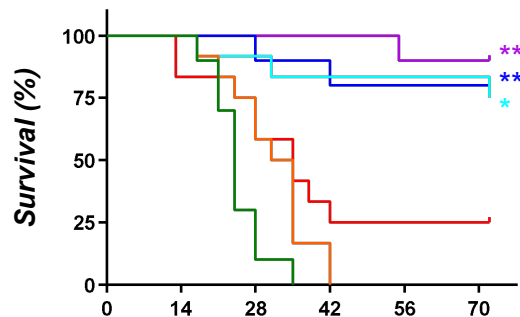
MBT-2 Bladder Cancer Model



Days after treatment initiation

- Control
- SRK-181-mIgG1 (10 mg/Kg/wk)
- Anti-PD1 (10 mg/Kg/2xwk)
- Anti-PD1 + SRK-181-mIgG1 (3 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (10 mg/Kg/wk)

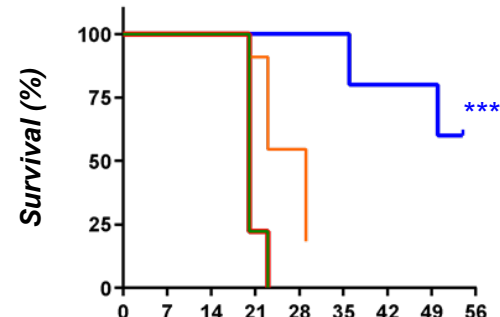
Cloudman S91 Melanoma Model



Days after treatment initiation

- Control
- SRK-181-mIgG1 (30 mg/Kg/wk)
- Anti-PD1 (10 mg/Kg/2xwk)
- Anti-PD1 + SRK-181-mIgG1 (3 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (10 mg/Kg/wk)
- Anti-PD1 + SRK-181-mIgG1 (30 mg/Kg/wk)

EMT6 Breast Cancer Model



Days after treatment initiation

- Control
- SRK-181-mIgG1 (10 mg/Kg/wk)
- Anti-PD1 (10 mg/Kg/2xwk)
- Anti-PD1 + SRK-181-mIgG1 (10 mg/Kg/wk)

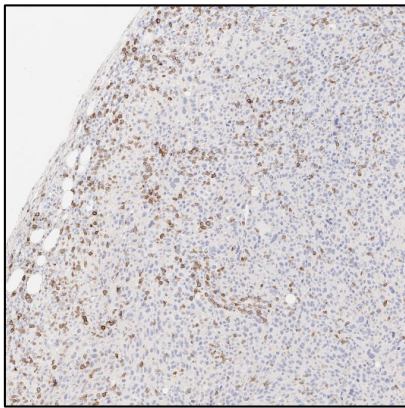
* P<0.05 Log-rank (Mantel-Cox test) vs. anti-PD1

**P<0.01

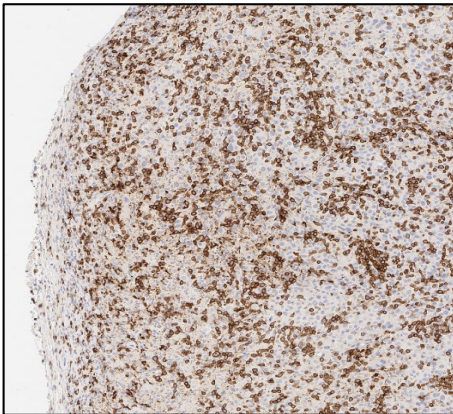
*** P<0.001

SRK-181-mIgG1 Combination Therapy Enabled Infiltration and Expansion of CD8⁺ T cells in Preclinical Bladder Cancer Model

Anti-PD1



Anti-PD1/SRK-181-mIgG1 (10 mg/kg)
led to increase in CD8+ cells



Combination treatment with SRK-181-mIgG1/anti-PD1 led to:

- Significant increase in effector T cells ($p < 0.05$)
 - Expansion of CD8⁺ population to an average of 34% of the tumor's immune cells from a control average of 3.5%
- Significant decrease in intratumoral immunosuppressive myeloid cells ($p < 0.05$)
 - Reduction in TAM/MDSC population to 14% of the tumor's immune cells from a control average of 47%
 - Reduction in MDSC population to 1.4% from 11% of CD45⁺ cells in the IgG control group

TGFβ1 Isoform Specificity of SRK-181 Improved Preclinical Toxicity Profile

Repeat dose pilot toxicology study in adult female Sprague Dawley rats

Microscopic observations in heart	Control	LY2109761	PanTGFβAb	SRK-181			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 SRK-181 serum concentration reached 2,300 µg/ml following 4 weekly doses of 100 mg/kg
- No SRK-181 related adverse effects were noted up to 100 mg/kg per week
- No cardiotoxicities (valvulopathy) were noted with SRK-181
- No observed adverse effect level (NOAEL) for SRK-181 was the highest dose evaluated (100 mg/kg QW)

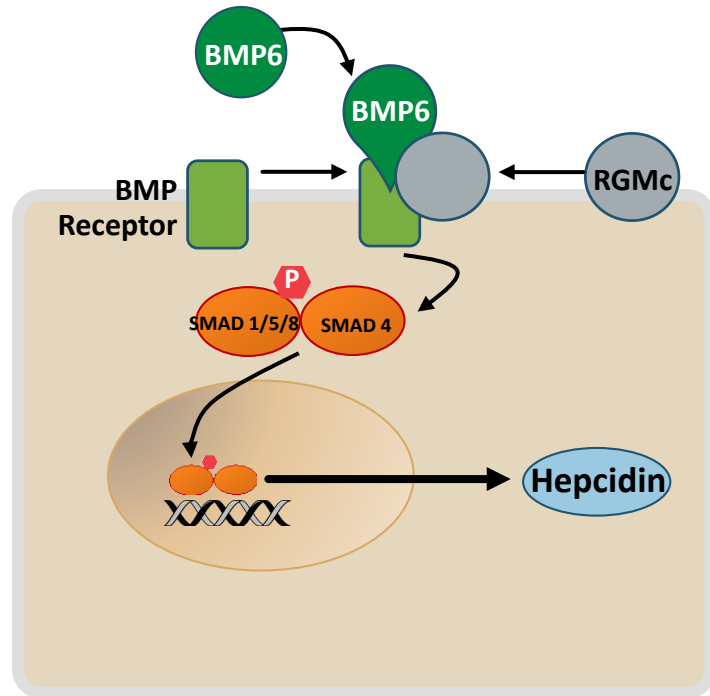
RGMc Program: Targeting the BMP6 Signaling Pathway



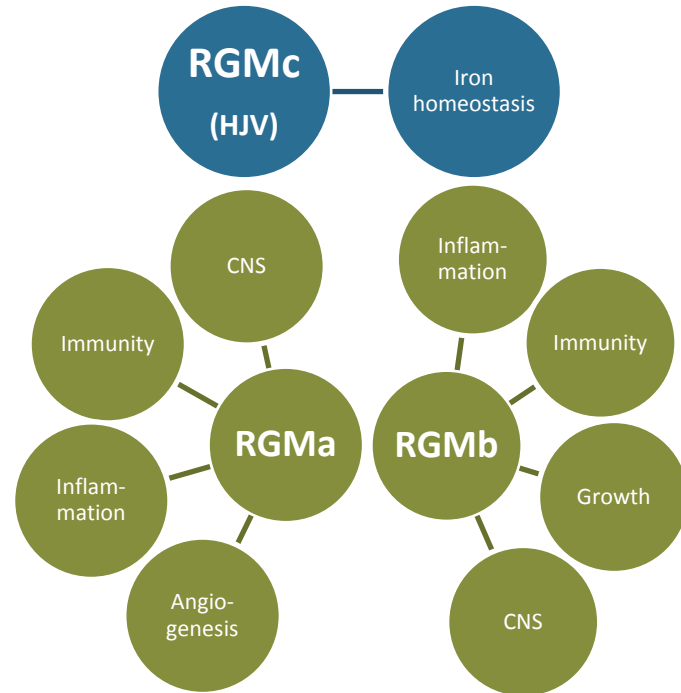
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Anti-RGMc Therapy: Rational Solution that Directly Addresses the Underlying Pathobiology of Iron-Restricted Anemias

Genetically validated pathway of iron regulation in humans

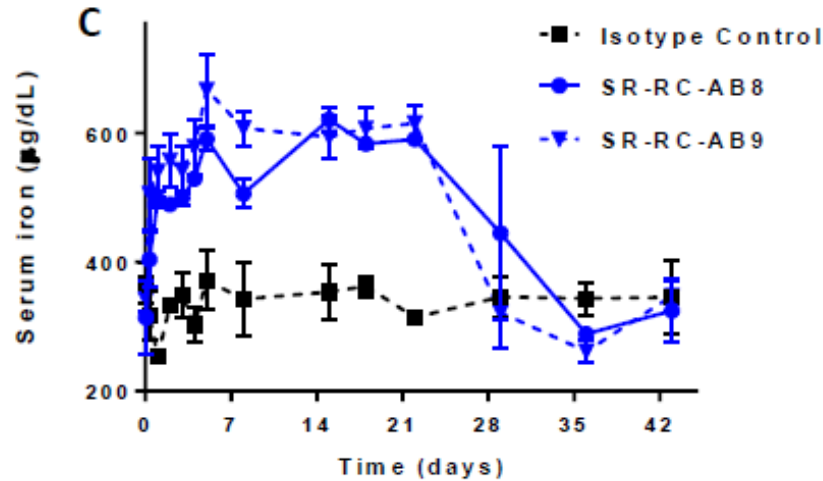


RGMa and RGMb play many different physiological roles

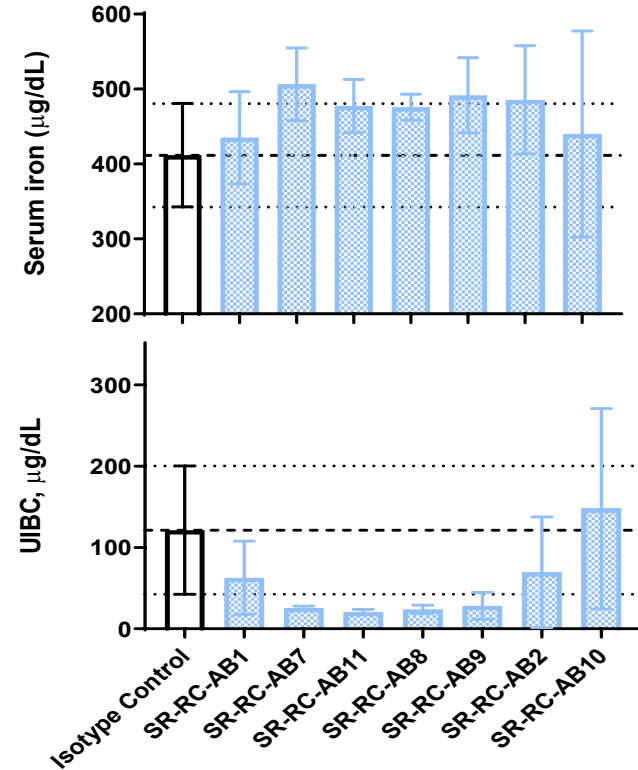


Scholar Rock's RGMc-Selective Antibodies Show Potent Increase in Serum Iron In Vivo

Antibodies showed up to 3 weeks prolonged increase in serum iron in SD rats (single 20 mpk dose)



Antibodies resulted in increases in serum iron and decreases in UIBC



Upcoming Key R&D Milestones

Spinal Muscular Atrophy (SMA)

- ✓ Initiate SRK-015 Phase 2 proof-of-concept SMA trial by the end of 1Q19
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- Continue to advance active discovery programs for context-dependent inhibition of TGFβ1

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Anemias

- Nominate product candidate in RGMc program in 2020

Appendix

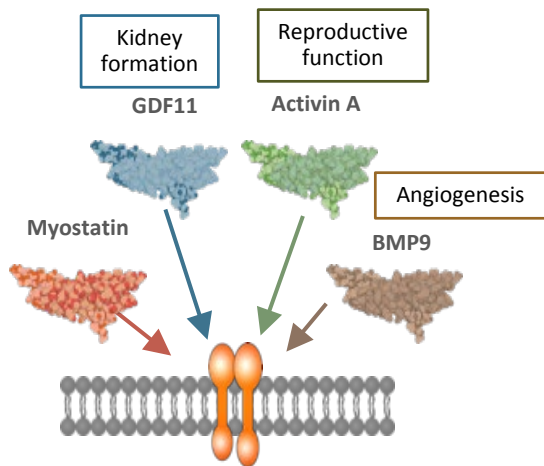


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Traditional Approaches Can Raise Significant Safety Concerns

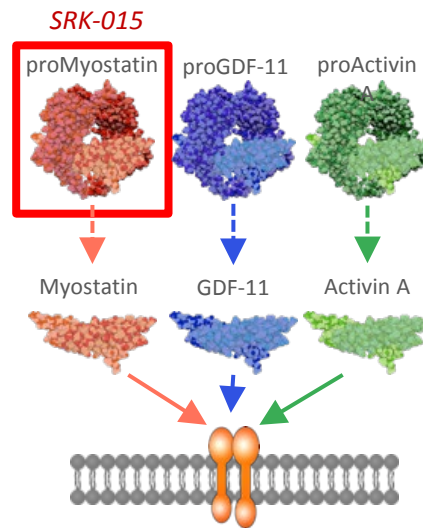
Traditional Approaches Lack Selectivity

- 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

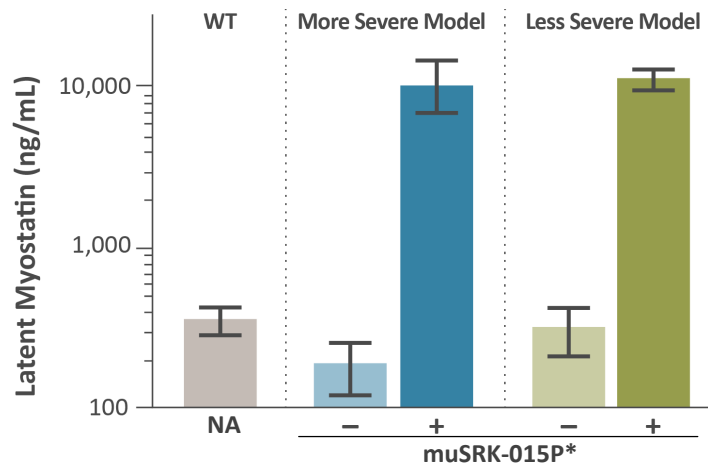


Scholar Rock Approach

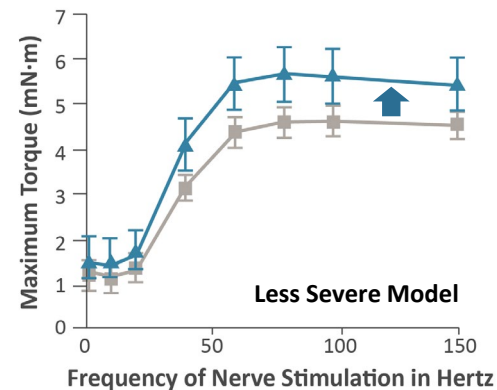
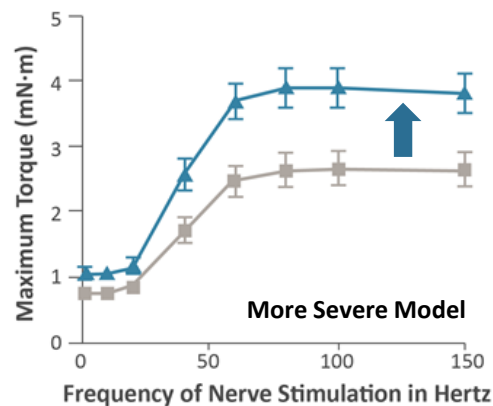
Exquisite Selectivity By Targeting Precursor Form of Myostatin



Review of Preclinical Data in SMN Δ 7 Mouse Models



- Achieved multi-fold increase in serum latent myostatin levels indicating target engagement
- Confirms presence of target in disease setting
- Lower latent myostatin levels in the SMA group may be attributable to reduced overall muscle mass



- ▲— SMN upregulator + muSRK-015P
- SMN upregulator only

Treatment improved muscle mass and strength

- Maximal torque of the plantar flexor muscle group increased:
 - More severe model: 44%-51%
 - Less severe model: 20%-30%

SRK-015 Phase 1 Trial Design

KEY OBJECTIVES OF PHASE 1

Evaluate the safety and tolerability, pharmacokinetics, and pharmacodynamics of SRK-015 IV

	SINGLE-ASCENDING DOSE (SAD)	MULTIPLE-ASCENDING DOSE (MAD)
Design	Double-blind, placebo-controlled 3:1 randomization	Double-blind, placebo-controlled 3:1 randomization
Subjects	40 Adult healthy volunteers (Ages 18-55)	26 Adult healthy volunteers (Ages 18-55)
Dosing	Single doses at: 1, 3, 10, 20, or 30 mg/kg	Q2W dosing for 3 doses at: 10, 20, or 30 mg/kg

SRK-015 Preclinical and Phase 1 Data Support Evaluation in SMA

Preclinical and translational data support myostatin as a drug target in SMA

- Confirmed presence of target in disease setting
- Achieved multi-fold increase in serum latent myostatin levels indicating target engagement
- Treatment of SMN Δ 7 mouse model led to improved muscle mass and strength

Phase 1 data in healthy volunteers showed robust target engagement and no apparent safety signals

- No dose-limiting toxicities identified up to highest evaluated dose of 30 mg/kg
- Serum half-life of 23-33 days supports planned evaluation of once every 4-week (Q4W) dosing in Phase 2
- Single dose of SRK-015 led to marked increases in serum concentrations of latent myostatin; no meaningful change observed with placebo
- **Target saturation:** peak latent myostatin levels plateaued starting with a single dose at 3 mg/kg
- **Durability of saturation:** plateau was sustained up to Day 140 after multiple doses at 20 mg/kg

Phase 1 results provide first proof-of-mechanism in humans of Scholar Rock's therapeutic approach of targeting the latent form of growth factors

SRK-015 Well Tolerated in Phase 1 Healthy Volunteer Trial

- **Well-tolerated with no apparent safety signals**
- **No dose-limiting toxicities identified up to highest evaluated dose of 30 mg/kg**
 - No discontinuations due to treatment-related adverse events (AEs)
 - No treatment-related SAE
 - No hypersensitivity reactions
- **Anti-drug antibody tests were negative in all SRK-015 treated subjects**
- **SAD cohort: AEs* were observed in 30% (9/30) SRK-015- vs. 50% (5/10) placebo-treated subjects**
 - Most frequently reported AE: headache
- **MAD cohort: AEs observed in 35% (7/20) SRK-015- vs. 67% (4/6) placebo-treated subjects**
 - Most frequently reported AE: postural dizziness
- **Single reported SAE of gallstone-induced pancreatitis**
 - Assessed by trial investigator as unrelated to SRK-015 treatment

*Term “adverse event” noted in this presentation refers to a treatment-emergent adverse event, which is defined as an AE with onset after administration of study drug through the final follow-up visit, or in the event that onset time precedes study drug administration, the AE increases in severity during the post-dosing follow-up period

Phase 1 Pharmacokinetic (PK) Data Support Infrequent Dosing

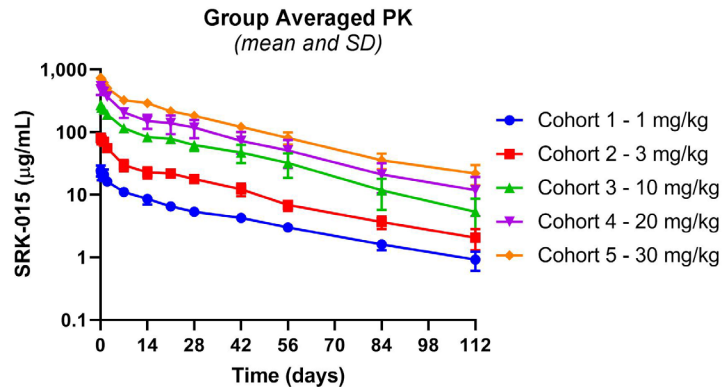
SRK-015 Displayed Well-Behaved, Linear PK Profile

- Minimal variability observed, consistent with that commonly observed with monoclonal antibodies
- Dose-proportional serum drug exposure

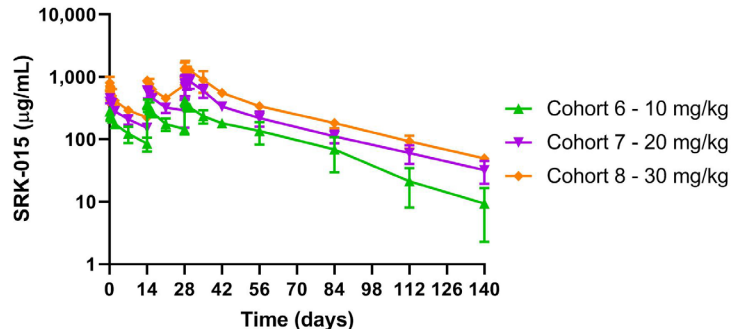
Half-Life Supports Infrequent Dosing

- Serum half-life of 23-33 days across SRK-015 dose groups
- Supports planned evaluation of once every 4-week (Q4W) dosing in Phase 2

Single-Ascending Dose



Multiple-Ascending Dose



Phase 1 Pharmacodynamic (PD) Data Demonstrate Robust and Sustained Target Engagement

Robust Target Engagement Observed

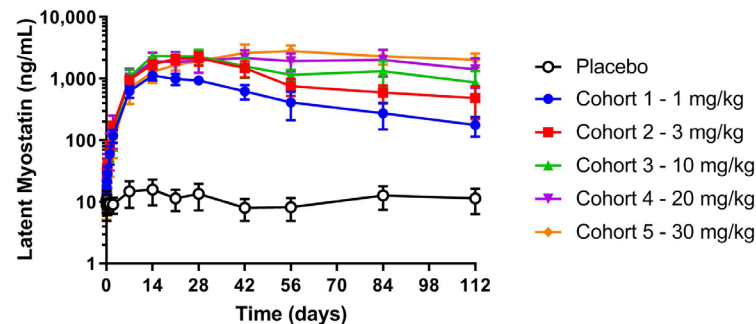
- Single dose of SRK-015 led to marked increases in serum concentrations of latent myostatin
- No meaningful change observed with placebo

Evidence Supports Durable Target Saturation

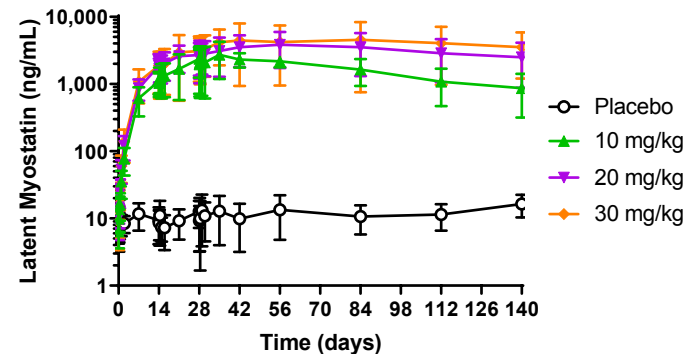
- Peak latent myostatin levels plateaued starting with a single dose at 3 mg/kg suggesting target saturation
 - Single dose at 1 mg/kg only attained approx. half of peak level
- Plateau was sustained demonstrating durability of effect:
 - Up to Day 84 after single dose at 20 mg/kg
 - Up to at least Day 140 after multiple doses at 20 and 30 mg/kg

First proof-of-mechanism in humans of Scholar Rock's therapeutic approach targeting the latent form of growth factors

Single-Ascending Dose



Multiple-Ascending Dose



TGFβ1 Plays Central Role in Multiple Diseases with Unmet Need



Oncology

Immuno-Oncology

Tumor-Directed Therapy

Myeloproliferative Disorders



Fibrosis

Upfront cash and equity investment:

\$80 million*

One-time preclinical milestone:

\$25 million

Additional milestones across 3 programs:

Up to \$1,425 million

High single- to low double-digit tiered royalties on net sales