



SCHOLAR ROCK

From New Insights to New Medicines

June 2019

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Building Value in All Dimensions

**Leveraging Strong Financial
Foundation**

Advancing Clinical Development



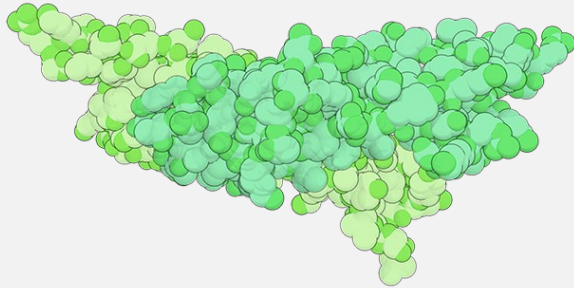
Executing Strategic Collaboration

Growing Innovative Pipeline

Nature's Growth Factor Activation Machinery

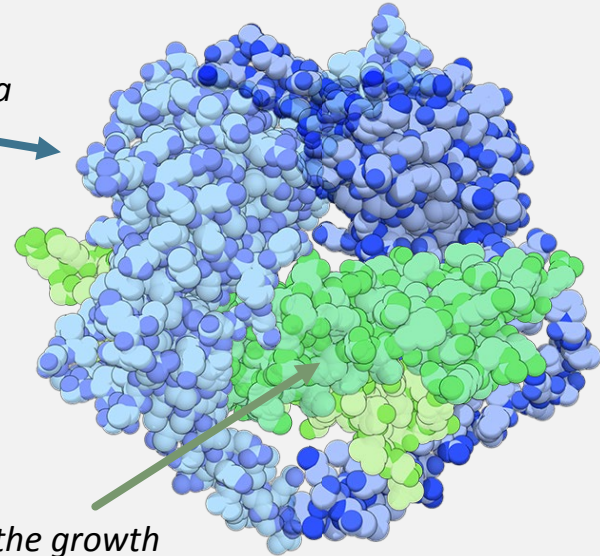
Mature TGF β 1

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

Robust Pipeline Portfolio

Program / Target		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						Preliminary PK/PD Data by End of 2019
	SRK-015	Myostatin-Related Disorders						Identify Next Indication in 2020
Latent TGFβ	SRK-181 (Context-Independent Latent TGFβ1)	Oncology/Immuno-oncology						Initiate Phase 1 Trial Mid-2020
	Context-Dependent Latent TGFβ1 / Immune Cell	Oncology/Immuno-oncology						
BMP6	BMP6 Signaling Pathway	Anemia						
PARTNERED PROGRAMS								
Latent TGFβ	Context-Independent Latent TGFβ1	Fibrosis					 GILEAD	
	Context-Dependent Latent TGFβ1 / LTBP1 & LTBP3	Fibrosis					 GILEAD	
	Undisclosed Program	Fibrosis					 GILEAD	
	Context-Dependent Latent TGFβ1 / GARP	Oncology/Immuno-oncology					Janssen Biotech, Inc	

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



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)*

SRK-015: Aligning Therapeutic Approach with Myostatin Biology

Scholar Rock's Guiding Principles for Neuromuscular Indication Selection

Younger population



Genetic disorder with onset in childhood

At least partially intact innervation and no structural muscle abnormalities



Partial neural connectivity and atrophied muscles that largely retain structural integrity

Need for increase in fast-twitch muscle fibers



Substantial deficit in fast-twitch fibers

Clinical trial endpoint driven by fast-twitch fiber function



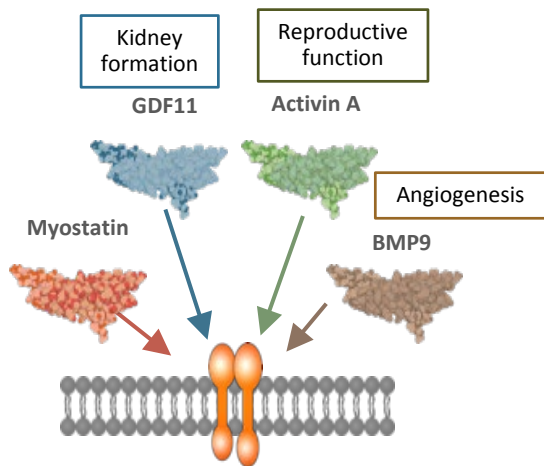
Fast-twitch fiber function has a prominent role in SMA outcome measures

Key Characteristics of Spinal Muscular Atrophy (SMA)

Traditional Approaches Can Raise Significant Safety Concerns

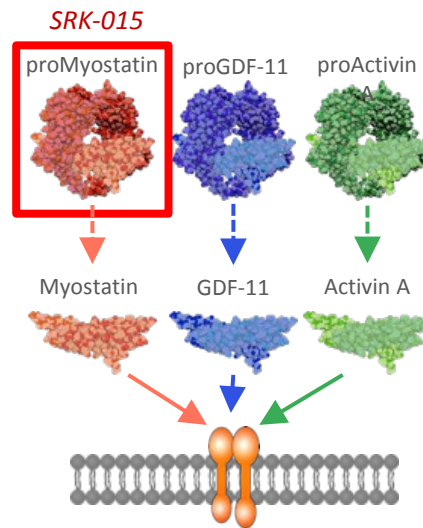
Traditional Approaches Lack Selectivity

- 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



Significant Unmet Need Remains Despite Current Therapies

SMN Upregulator Therapies

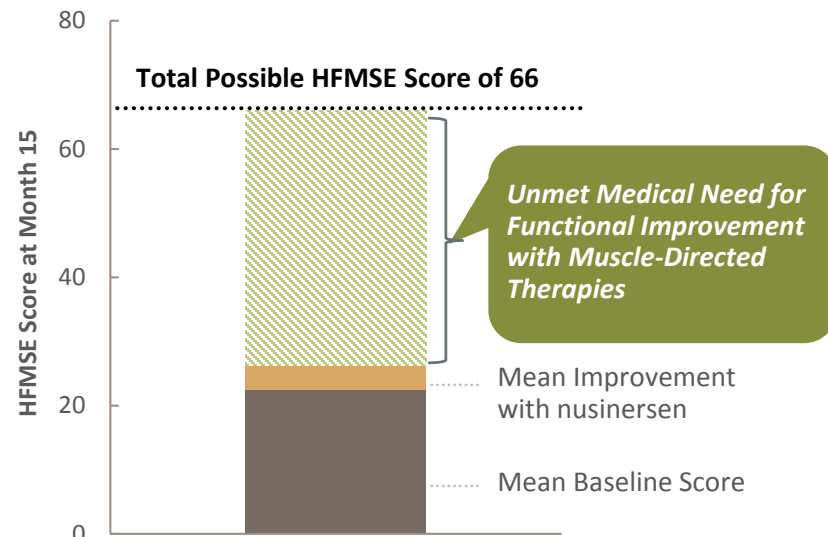
Address SMN deficiency to prevent further motor neuron deterioration

Muscle-Directed Therapies (SRK-015)

Act directly on muscle with aim to improve functional performance

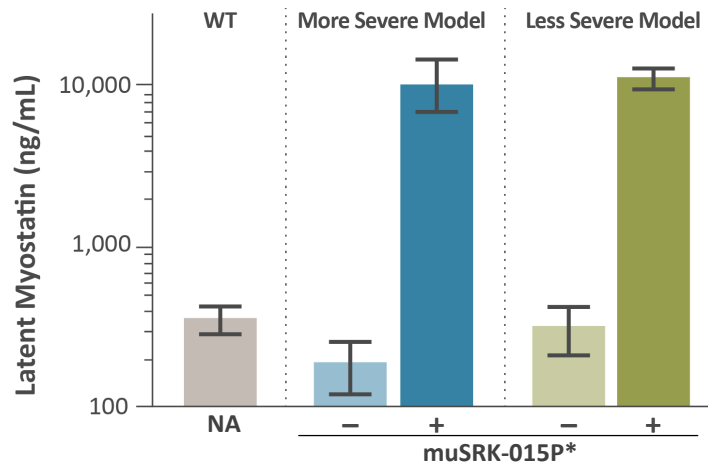
SRK-015 has the potential to drive functional performance across a range of severity observed in SMA either as a monotherapy or in conjunction with any SMN upregulator/corrector therapy

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

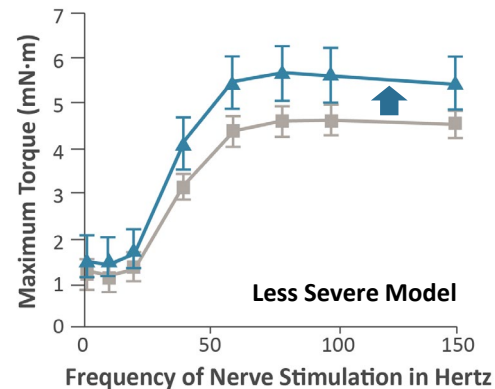
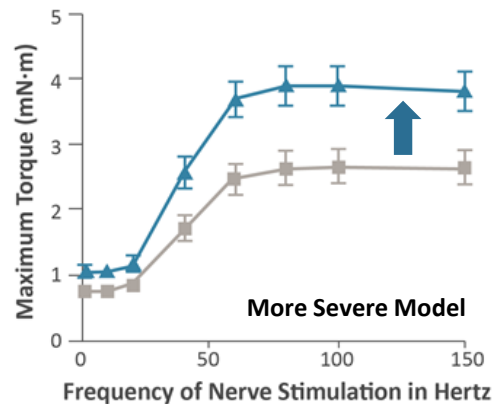


Mean improvement in HF MSE score experienced by patients with later-onset SMA in the Phase 3 CHERISH clinical trial of nusinersen

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 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

Pharmacokinetic (PK) Data Support Infrequent Dosing

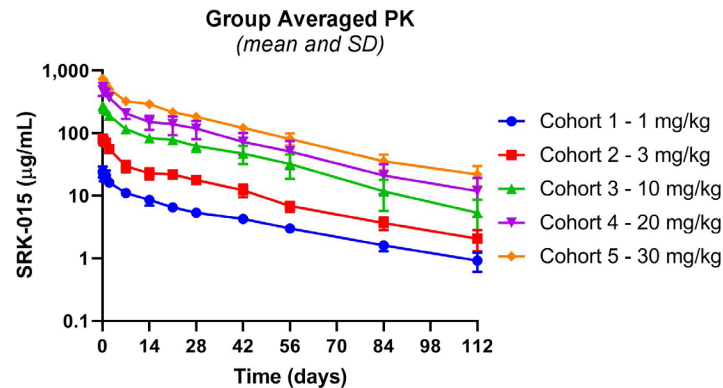
SRK-015 Displayed Well-Behaved, Linear PK Profile

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

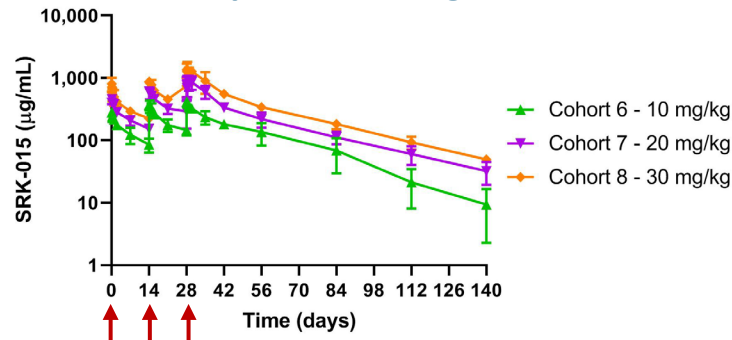
Half-Life Supports Infrequent Dosing

- 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



PD Data Demonstrate Robust and Sustained Target Engagement

Robust Target Engagement Observed

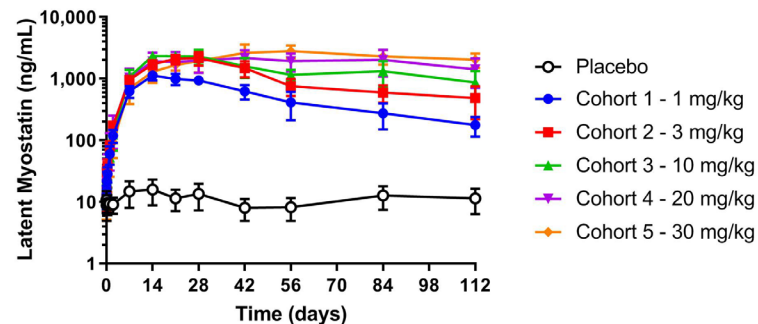
- Single dose of SRK-015 led to marked increases in serum concentrations of latent myostatin
- No meaningful change observed with placebo

Evidence Supports Durable Target Saturation

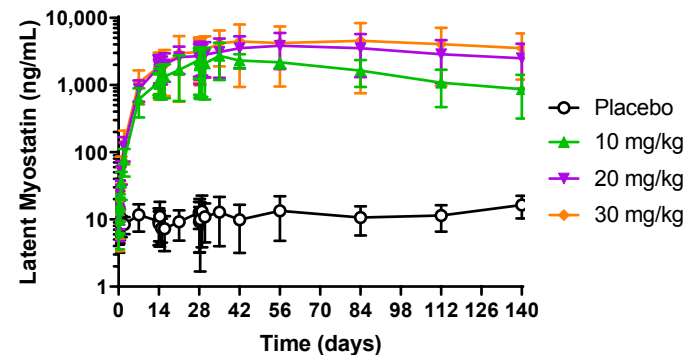
- Peak latent myostatin levels plateaued starting with a single dose at 3 mg/kg suggesting target saturation
 - Single dose at 1 mg/kg only attained approx. half of peak level
- Plateau was sustained demonstrating durability of effect:
 - Up to Day 84 after single dose at 20 mg/kg
 - Up to at least Day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

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

Single-Ascending Dose



Multiple-Ascending Dose



SRK-015 Target Profile in SMA

GOALS

EVIDENCE TO DATE

Effectively increase motor function to drive clinically meaningful outcomes

- ✓ Translational/preclinical data support myostatin as a drug target in SMA
- ✓ Preclinical data demonstrate potential for substantial increases in muscle strength
- ✓ Phase 1 PD data demonstrate SRK-015 can successfully engage the target in a durable fashion

Safety profile to enable chronic dosing, including in pediatric populations

- ✓ Well-tolerated with no apparent safety signals based on Phase 1 data
- ✓ Binds myostatin precursors with high selectivity in vitro

Low drug administration burden to offer broad accessibility

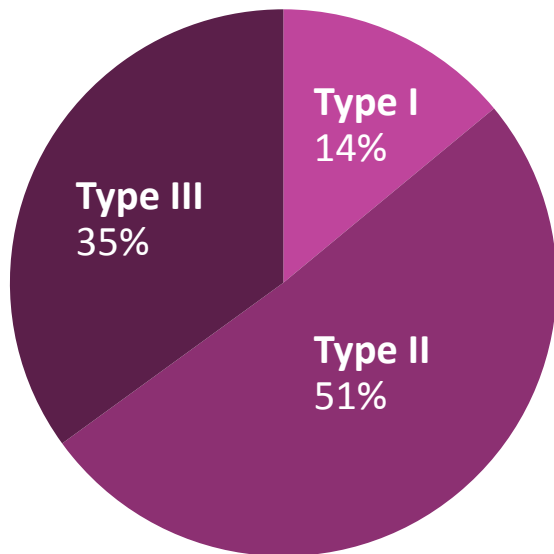
- ✓ Minimally invasive route of administration (IV)
- ✓ PK and PD data support an infrequent dosing regimen (e.g. once every 4 weeks)

Emerging evidence supports investigating the safety and efficacy of SRK-015 in SMA

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*

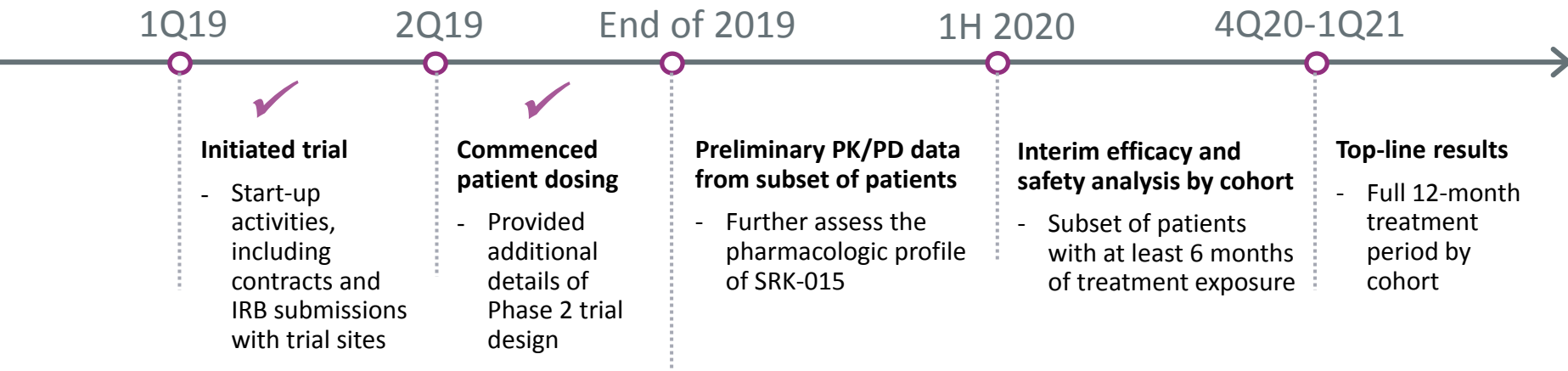
*Potential to use SRK-015
as monotherapy or in
conjunction with SMN
upregulators*

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

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



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 and Fibrosis



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TGFβ1 Plays Central Role in Multiple Diseases with Unmet Need



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Oncology

Immuno-Oncology

Tumor-Directed Therapy

Myeloproliferative Disorders



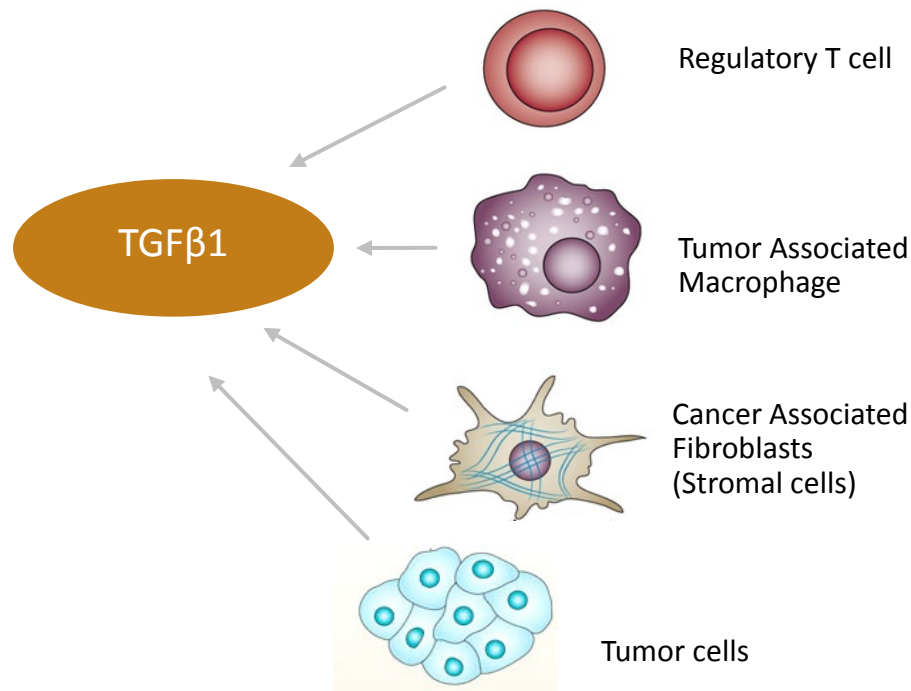
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Fibrosis



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

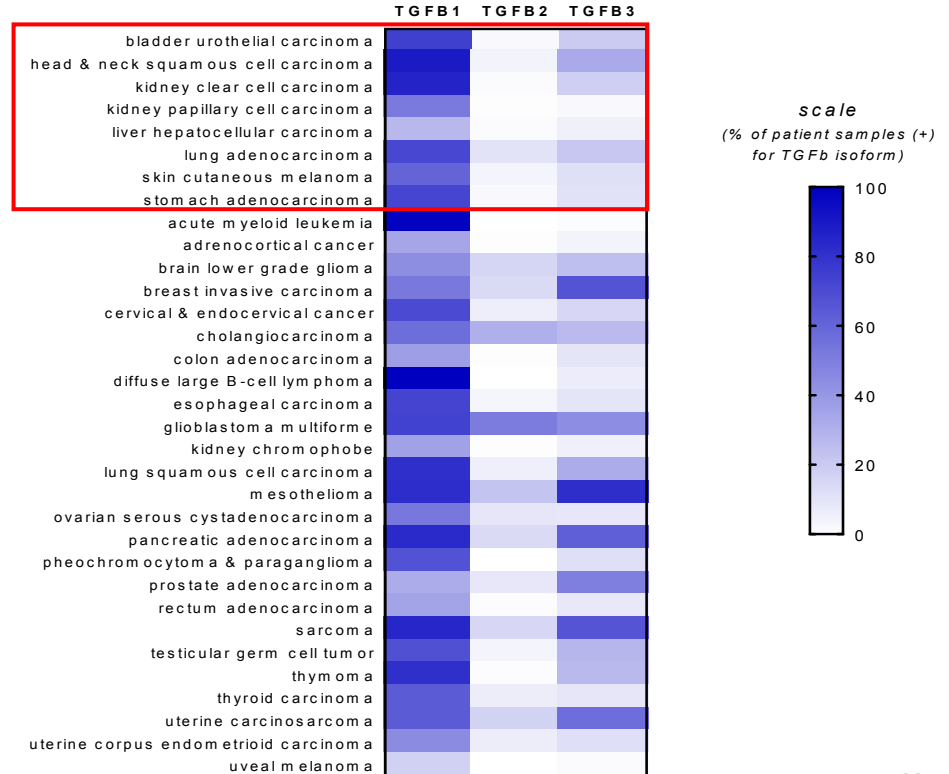
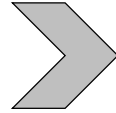
Sanjeev Mariathasan^{1*}, Shannon J. Turley^{1*}, Dorothee Nickles^{1*}, Alessandra Castiglioni¹, Kobe Yuen¹, Yulei Wang¹, Edward E. Kadel III¹, Hartmut Koeppen¹, Jillian L. Astarita¹, Rafael Cubas¹, Suchit Jhunjhunwala¹, Romain Banchereau¹, Yagai Yang¹, Yinghui Guan¹, Cecile Chalouni¹, James Ziai¹, 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-PDL1 (atezolizumab)
- TGFβ1 creates 'immune excluded' tumor microenvironment
- Anti-TGFβ antibody enhances anti-PDL1 treatment response in syngeneic EMT6 tumor model

TGFβ1 is the Predominant Isoform in Most Human Tumors

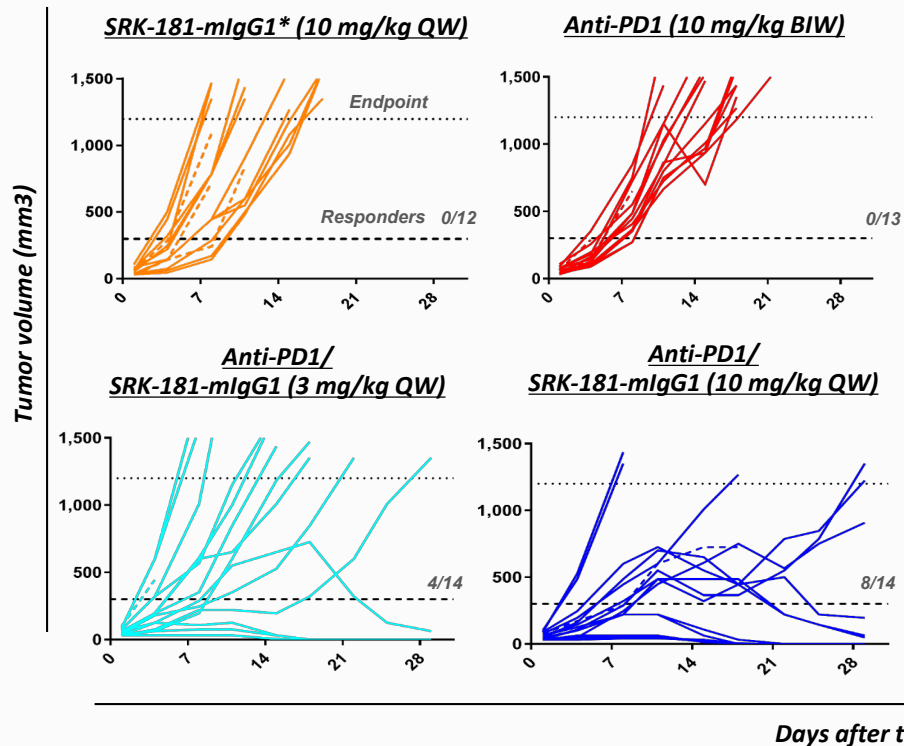
The Cancer Genome Atlas RNAseq analysis: >10,000 samples spanning 33 tumor types

- 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

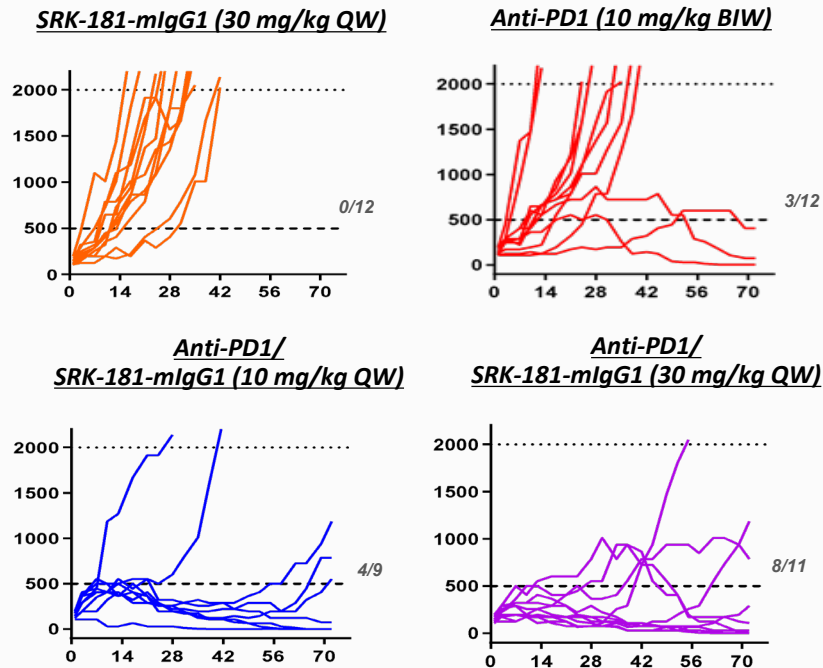


TGF β 1 Blockade with SRK-181-mlgG1 Renders Preclinical Tumor Models Susceptible to Anti-PD1 Therapy

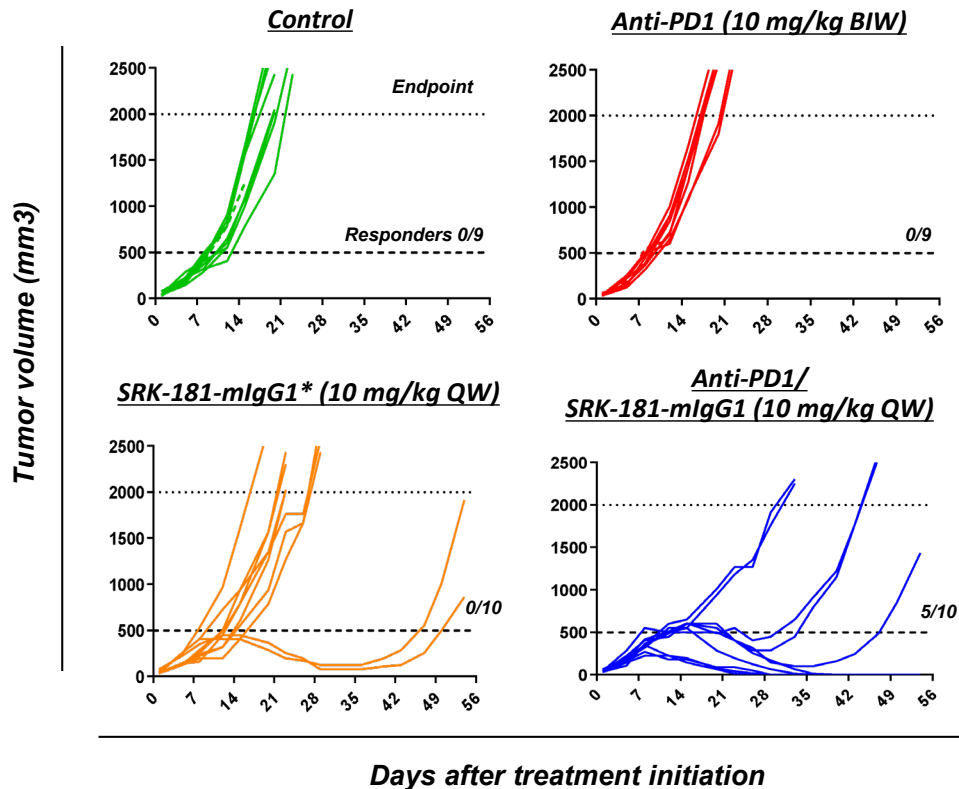
Bladder Cancer



Melanoma



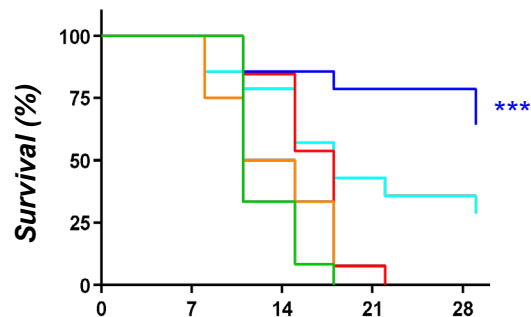
Inhibiting TGF β 1 Alone is Sufficient to Sensitize Preclinical TGF β 1/3-Expressing Breast Cancer Model



- 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 Leads to Significant Survival Benefit in Preclinical Tumor Models

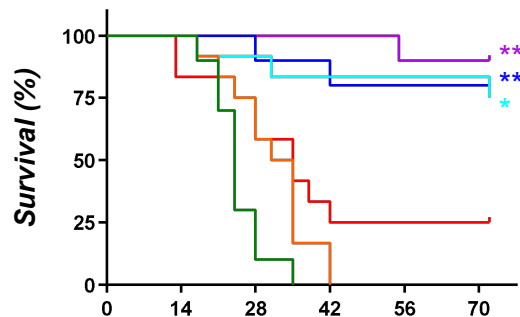
MBT-2 Bladder Cancer Model



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)

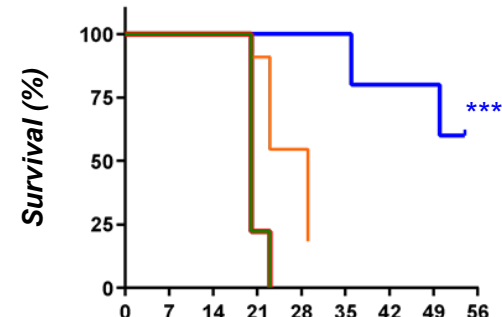
Cloudman S91 Melanoma Model



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

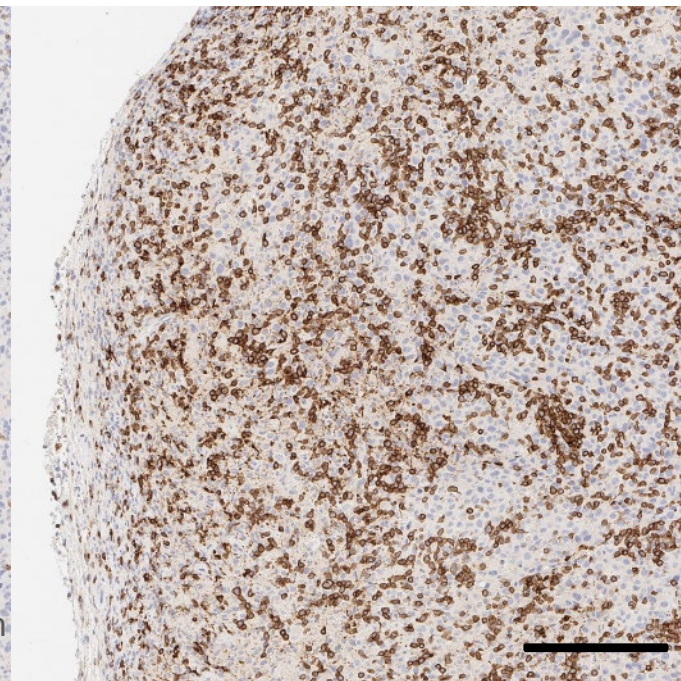
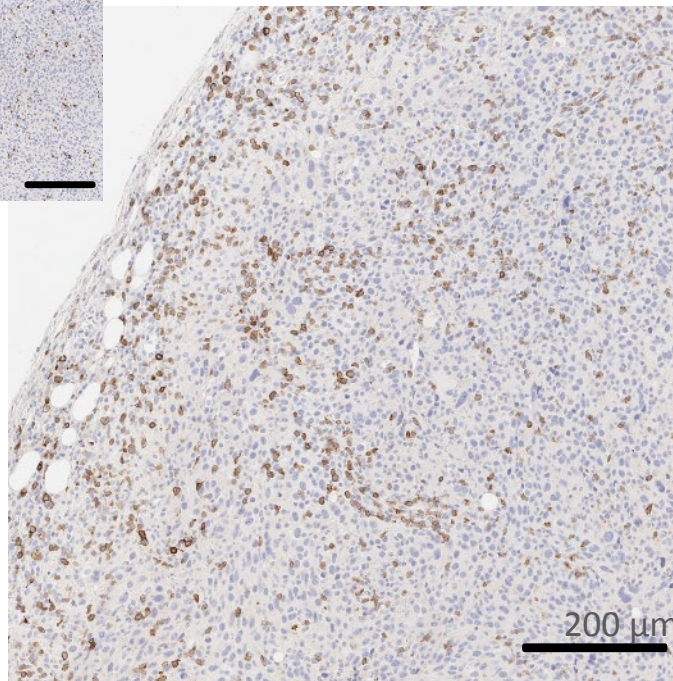
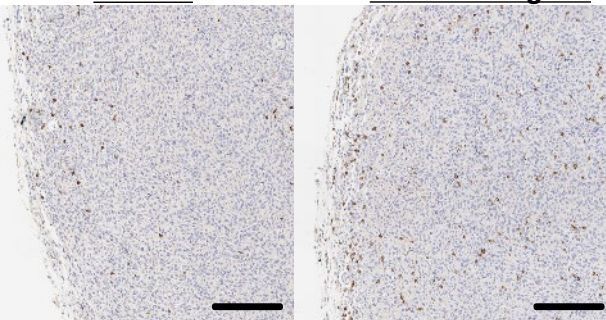
SRK-181-mIgG1 Combination Therapy Enables Infiltration and Expansion of CD8⁺ T cells in Preclinical Tumor Model

Control

SRK-181-mIgG1*

Anti-PD1

Anti-PD1/
SRK-181-mIgG1 (10 mg/kg)



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 SRK-181 Results in 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)

SRK-181: Advancing Development for Treatment of Cancers Resistant to Checkpoint Blockade Therapies (CBTs)

SRK-181 is a fully human antibody designed to bind to, and prevent the activation of, latent TGFβ1 with high affinity and high selectivity

TGFβ signaling



Implicated as a culprit in primary resistance to CBTs

Translational data analyses



TGFβ1 expression is prominent in many human tumor types for which CBTs is approved or showed clinical activity

Clinical correlation and preclinical model data



TGFβ1 excludes effector cell entry into the tumor and limits immune system access to tumor cells

Preclinical studies in syngeneic mouse tumor models resistant to CBT



Combination of SRK-181-mIgG1* with anti-PD1 led to tumor regression/control and significant survival benefit, including in models that express both TGFβ1 and TGFβ3

28-day pilot toxicology study in adult rats



SRK-181 showed no observed drug-related toxicity up to a weekly dose of 100 mg/kg for 4 weeks

Highlights of Strategic Fibrosis Collaboration with Gilead



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Responsible for antibody discovery and preclinical research thru product candidate nomination for three TGFβ programs

Retains exclusive worldwide rights to develop certain TGFβ antibodies for oncology and cancer immunotherapy

Collaborating
to Develop Innovative
Therapies for Fibrotic
Diseases



GILEAD

Upon option exercise, responsible for preclinical and clinical development and commercialization

Upfront cash and equity investment:
\$80 million*

One-time preclinical milestone:
\$25 million

Additional development, regulatory, and commercial milestones across 3 programs:
Up to \$1,425 million

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

Upcoming Key R&D Milestones

SRK-015

- ✓ Initiate Phase 2 SMA proof-of-concept trial by the end of 1Q19
- ✓ Commence patient dosing in 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
- Continue to evaluate selective inhibitors of myostatin activation in multiple disease models
- Identify next indication in 2020
- Announce Phase 2 trial read-outs:
 - Preliminary PK/PD analysis by end of 2019
 - Interim efficacy and safety analysis at 6 months in 1H20
 - Top-line results of 12-month treatment period 4Q20-1Q21

TGFβ1 Inhibitor

- Advance cancer immunotherapy product candidate, SRK-181, into a Phase 1 trial mid-2020
- Continue to advance active discovery programs for context-dependent inhibition of TGFβ1
- Conduct fibrosis discovery and preclinical studies in partnership with Gilead

Building Value in All Dimensions

**Leveraging Strong Financial
Foundation**

Advancing Clinical Development



Executing Strategic Collaboration

Growing Innovative Pipeline