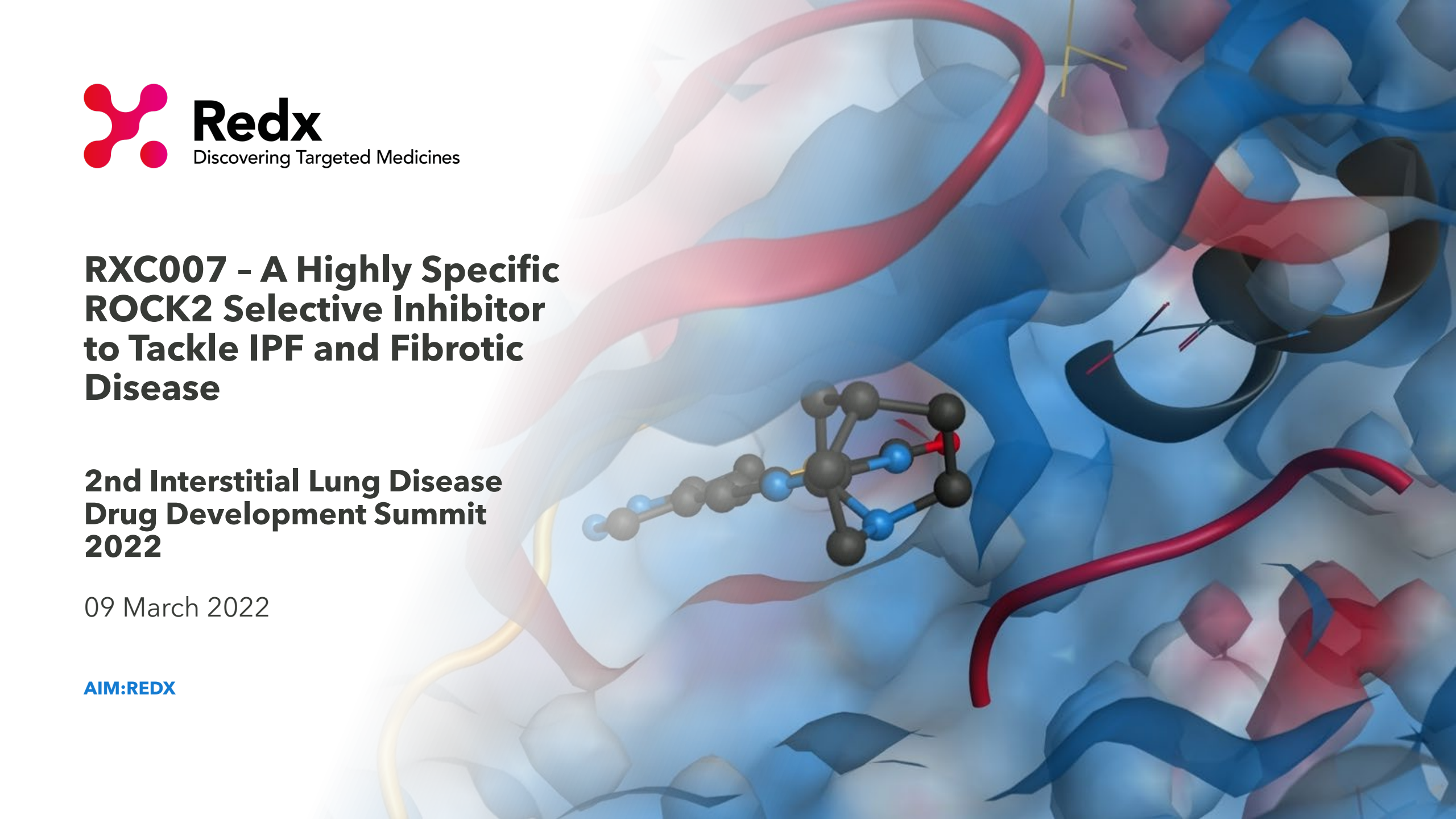
Redx
Discovering Targeted Medicines

RXC007 – A Highly Specific ROCK2 Selective Inhibitor to Tackle IPF and Fibrotic Disease

2nd Interstitial Lung Disease Drug Development Summit 2022

09 March 2022

AIM:REDX



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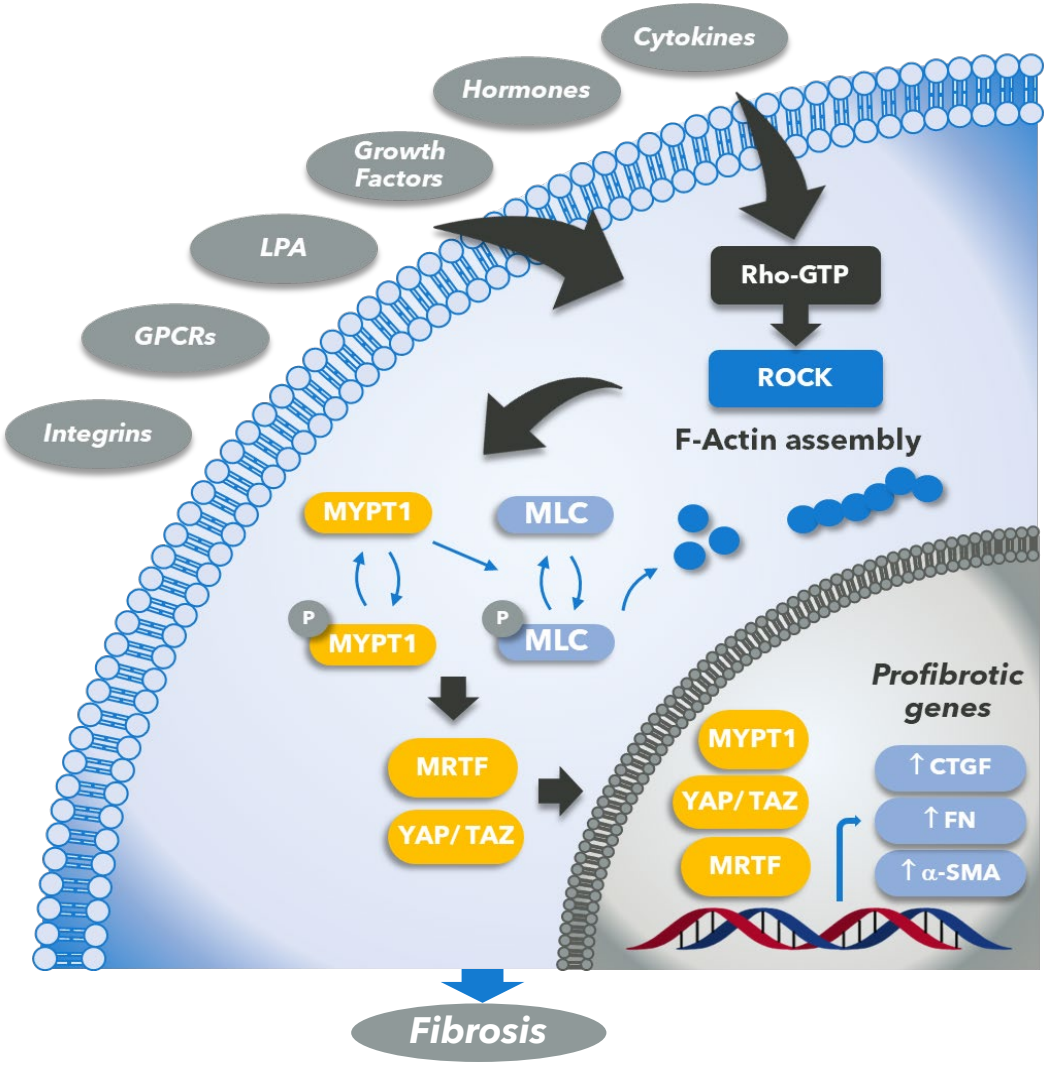
Agenda

- ROCK and ROCK2 selective inhibition
- Rationale for ROCK2 in Interstitial Lung Diseases
- RXC007 – A highly specific ROCK2 selective inhibitor to tackle IPF and fibrotic disease
- RXC007 in *in vivo* and *ex-vivo* lung models
- RXC007/0001: A randomised, double-blind, placebo-controlled, single-ascending dose and multiple dose, first-in-human, Phase 1
- Summary

IPF: Idiopathic pulmonary fibrosis; ROCK: Rho associated protein kinase

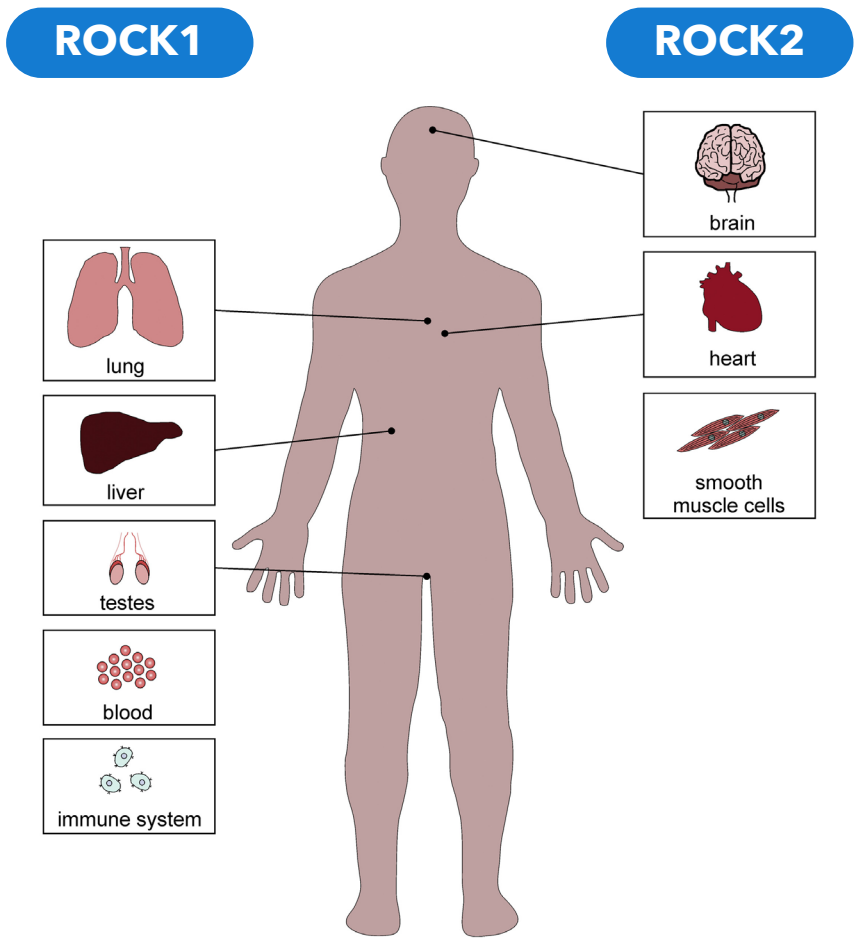
Rho-associated Coiled-coil Containing Kinases (ROCKs)



- Members of the AGC (protein kinase A, G and C, PKA/PKG/PKC) family of serine/threonine kinase family
- Originally identified as downstream effectors of RhoA
- ROCKs facilitate RhoA-induced stress fiber formation and focal adhesion assembly
- ROCKs are expressed in both invertebrates and vertebrates
- RhoA/ROCK signaling is closely involved in regulating cell morphology, growth, migration, and apoptosis
- Activated GTP-bound RhoA can further activate ROCK to phosphorylate several substrates
- Substrates involved in autophagy, cell survival & apoptosis, vesicle dynamics, cytoskeleton regulation, cell growth & regeneration, cell shape & motility

ROCK: Rho associated protein kinase

Two Isoforms of ROCK, ROCK1 (ROCKβ) and ROCK2 (ROCKα)



- Two isoforms of ROCK, ROCK1 (ROCKβ) and ROCK2 (ROCKα)
- Selective ROCK isoform inhibition is challenging because of high degree of sequence homology
  - 65% amino acid sequences in common
  - 92% homology within their kinase domains
- ROCK1/2 inhibitors deliver an anti-fibrotic effect in preclinical studies but induce hypotension, limiting further clinical development
- Selective ROCK2 inhibitors can inhibit fibrosis without inducing hypotension

ROCK: Rho associated protein kinase

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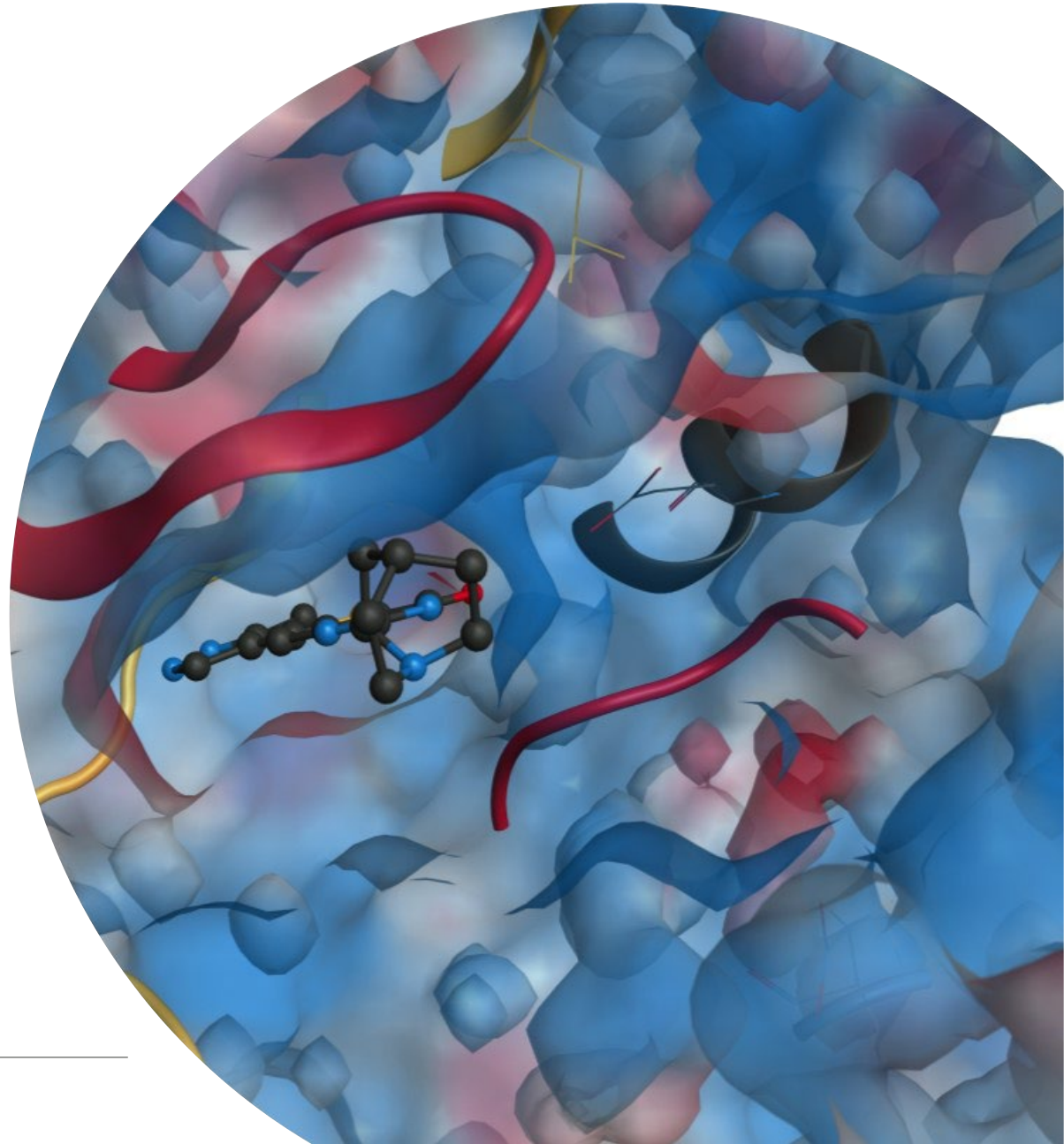
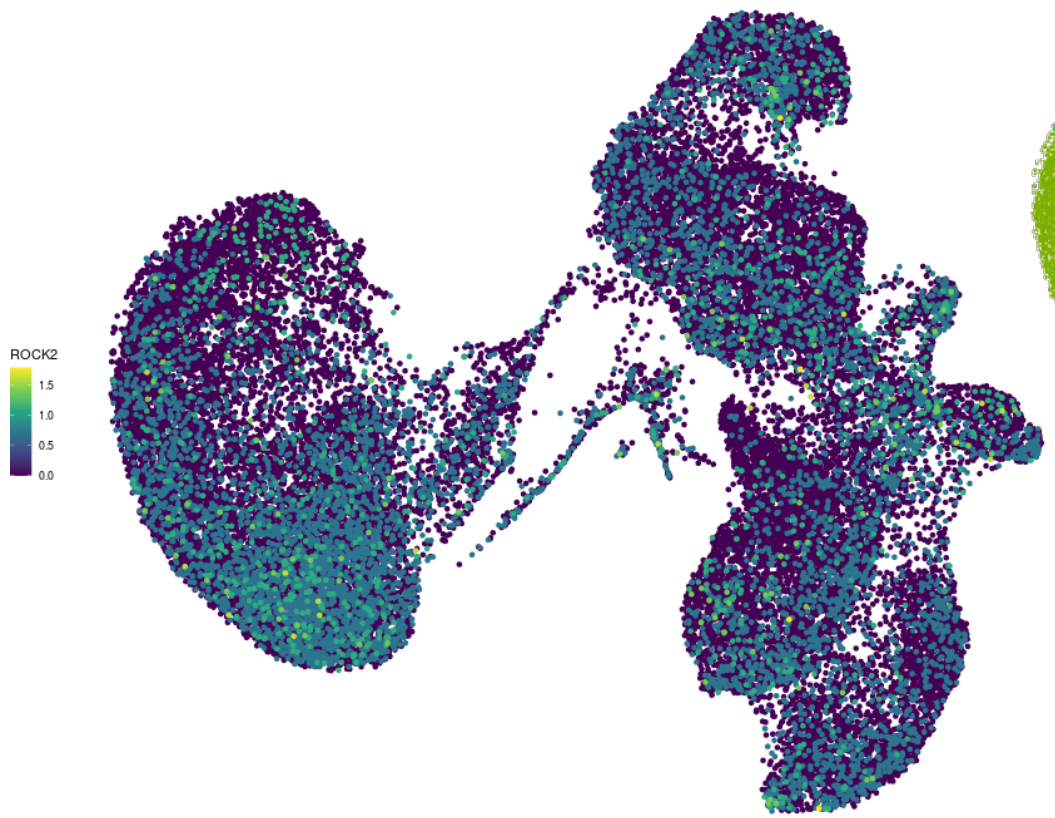
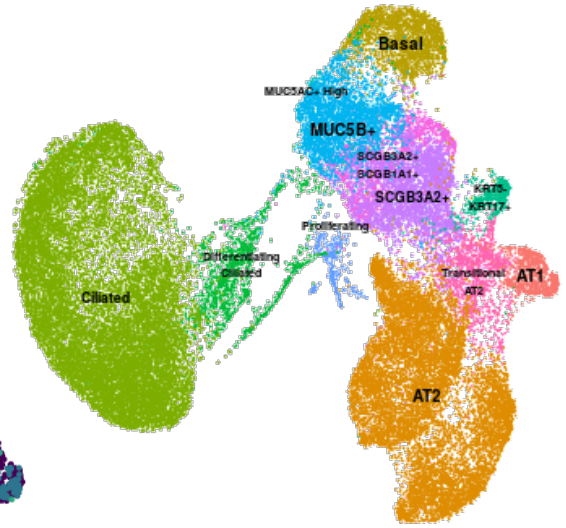
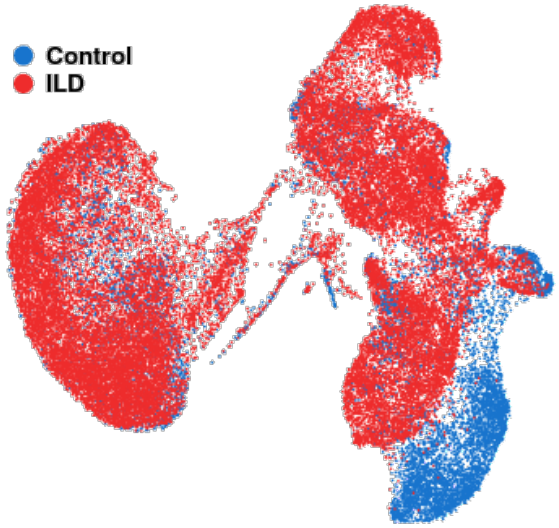
Rationale for ROCK2 inhibition in Interstitial Lung Diseases



High Expression of ROCK2 in Epithelial Cells in Interstitial Lung Diseases





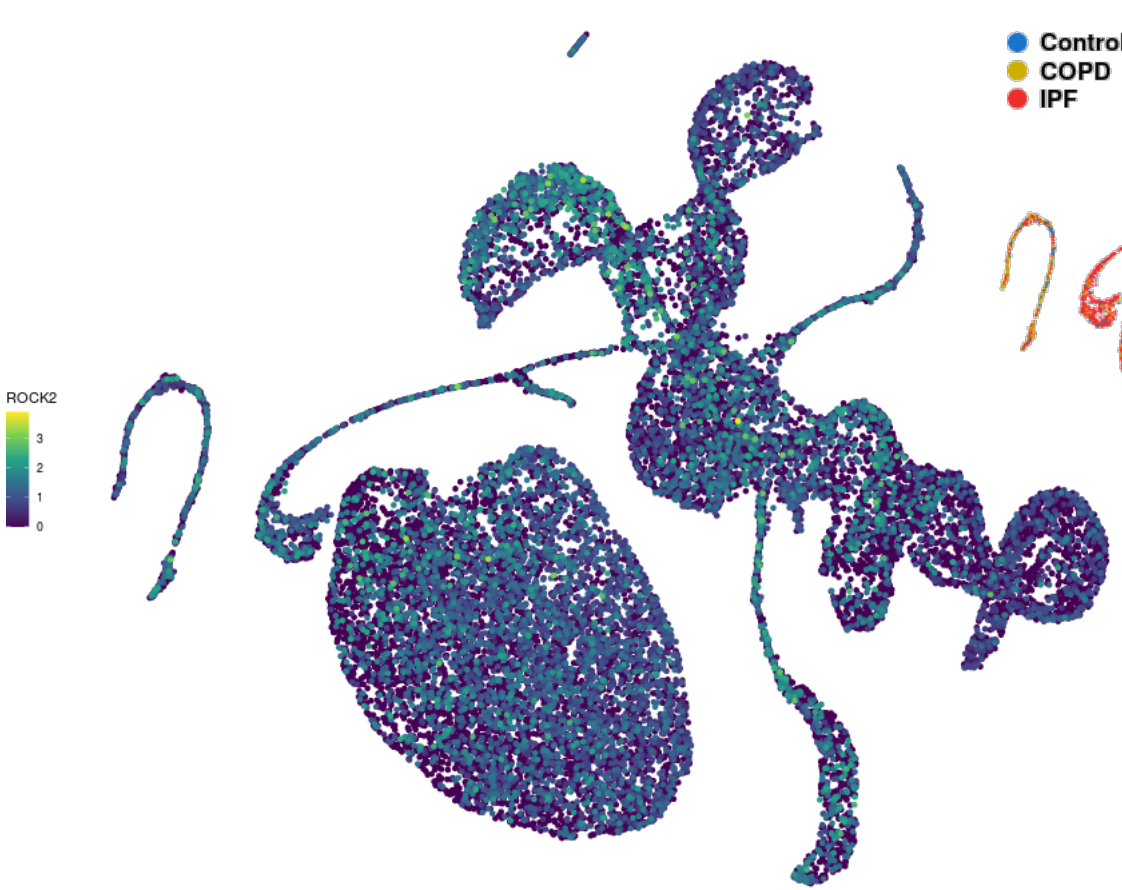


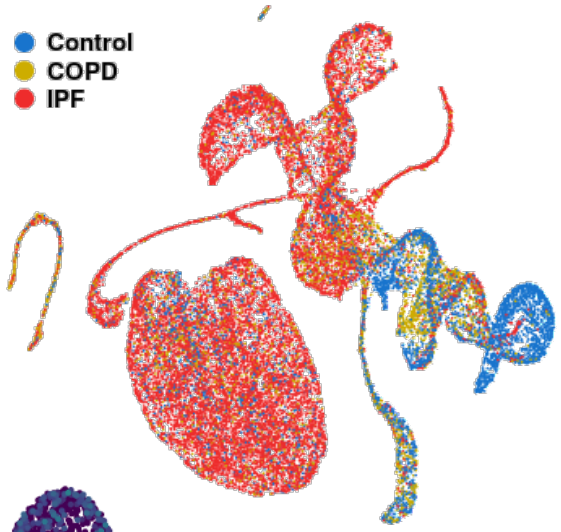
Disease	Subjects
cHP	2
Control	10
IPF	12
NSIP	3
sarcoidosis	2
Unclassifiable ILD	1

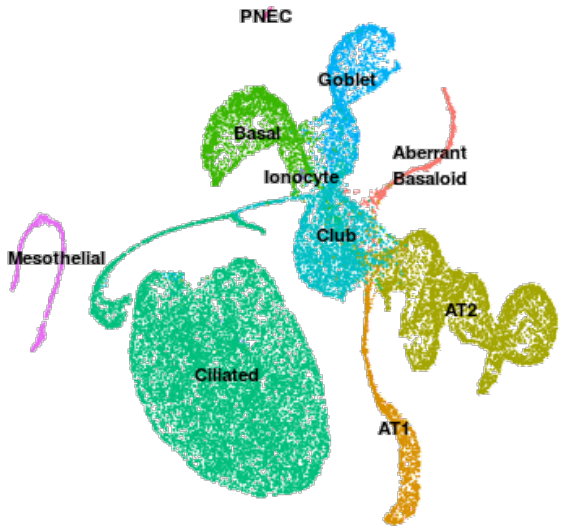
Banovich/Kropski database IPF cell atlas

cHP: Chronic hypersensitivity pneumonitis; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; NSIP: Nonspecific interstitial pneumonia; ROCK: Rho associated protein kinase

High Expression of ROCK2 in IPF Epithelial cells





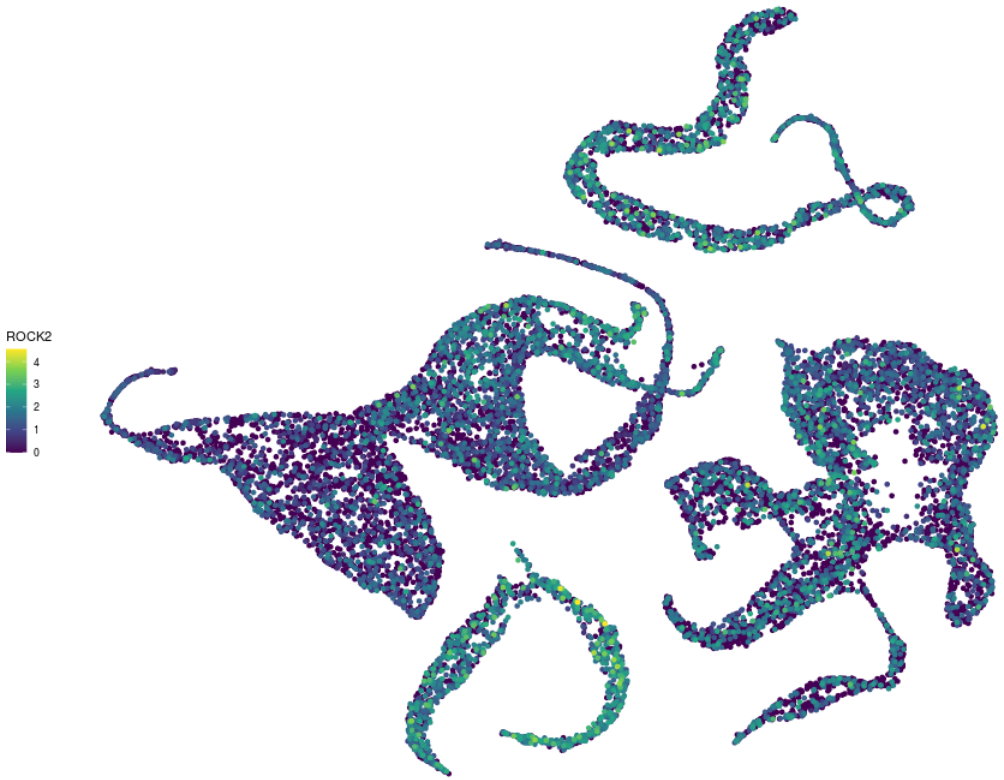


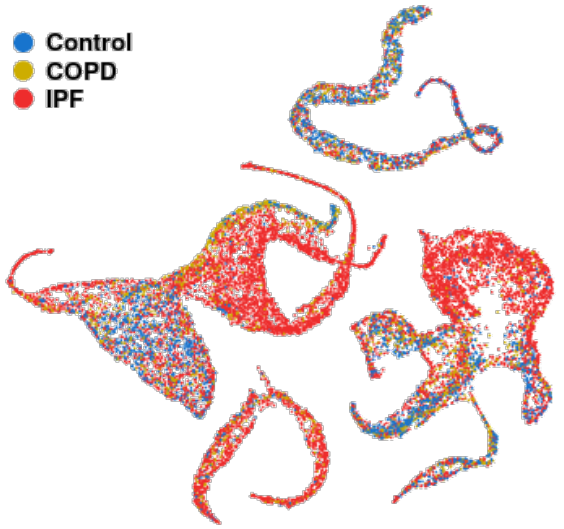
Disease	Subjects
Control	29
COPD	18
IPF	32

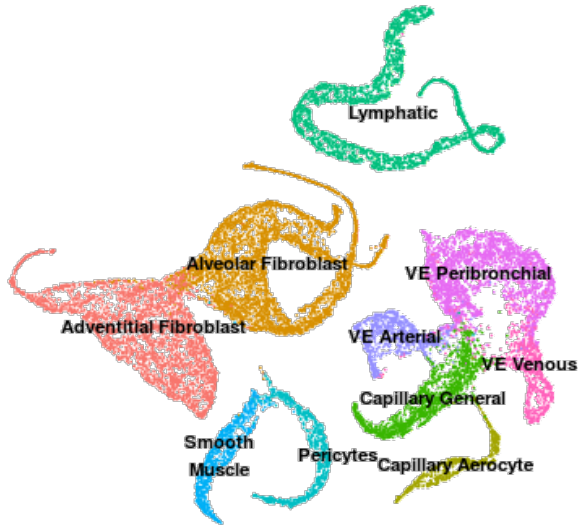
Kaminski/Rosas database IPF cell atlas
COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis; ROCK: Rho associated protein kinase

Myofibroblasts, Smooth Muscle, Pericytes and Lymphatic Cells all show Increased ROCK2 Expression in IPF

High expression of ROCK2 in IPF Stromal cells; IPF highly present in myofibroblasts, smooth muscles, pericytes, VE peribronchial







Disease	Subjects
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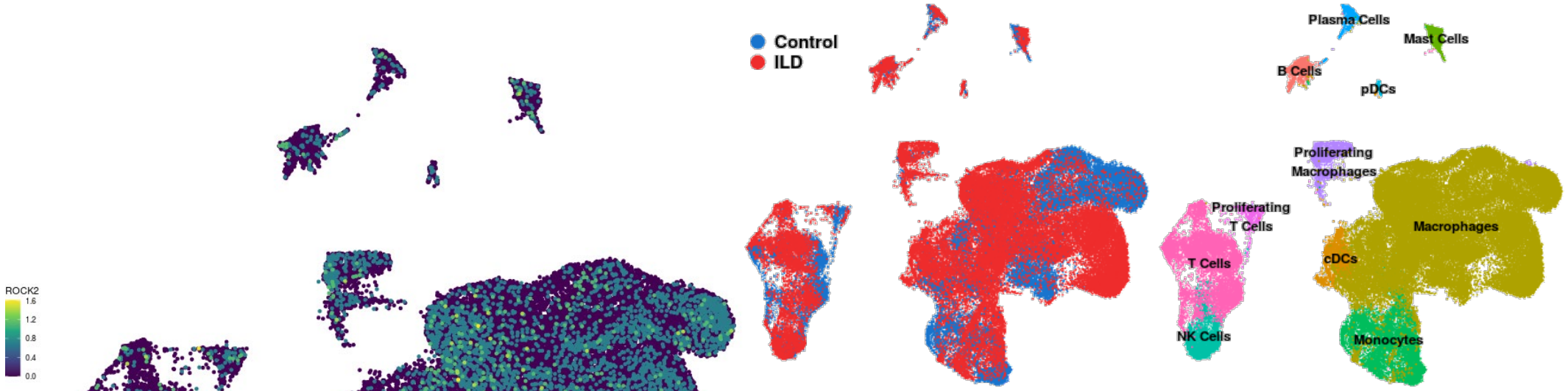
Kaminski/Rosas database IPF cell atlas – single cell RNAseq data – Stromal
COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis; ROCK: Rho associated protein kinase; VE: Vascular endothelial

High Expression of ROCK2 in Macrophages, Monocytes in Interstitial Lung Diseases

High expression of ROCK2 in Immune cells in Interstitial Lung Diseases



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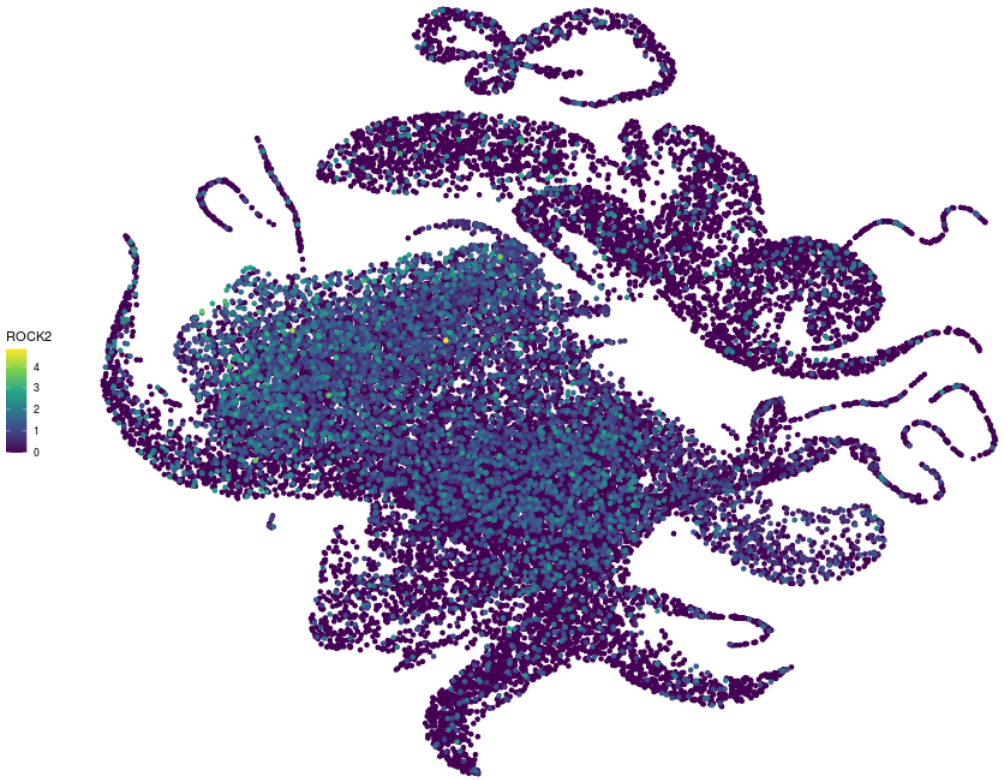
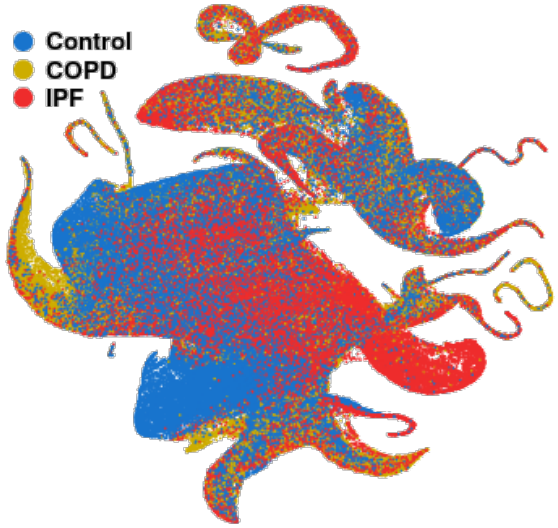
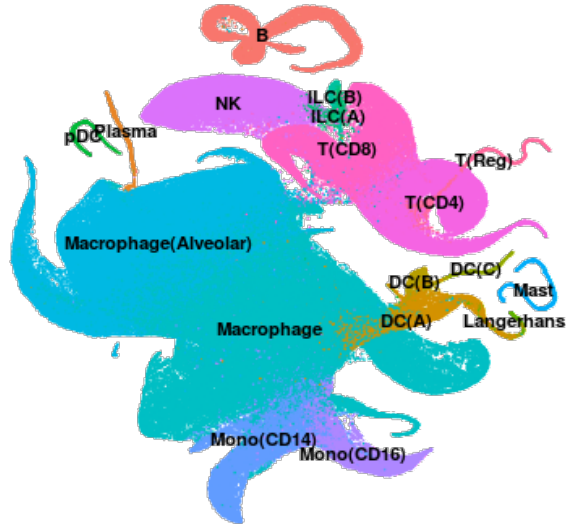
cHP: Chronic hypersensitivity pneumonitis; ILD: Interstitial lung disease; IPF: Idiopathic pulmonary fibrosis; NSIP: Nonspecific interstitial pneumonia; ROCK: Rho associated protein kinase

High ROCK2 Expression in Both IPF and Normal Lung Macrophages







Disease	Subjects
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COPD	18
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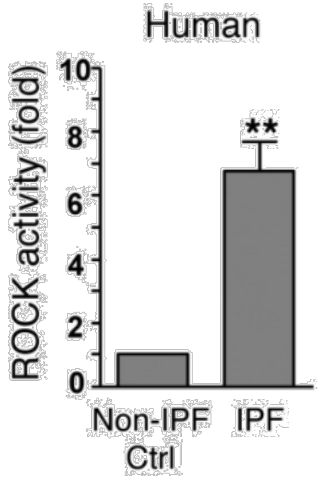
Kaminski/Rosas database IPF cell atlas
COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis; ROCK: Rho associated protein kinase

Increased Expression and Activation of ROCK2 and pMYPT1 in IPF Bronchial Epithelial Cells & Fibroblasts

Strong literature rationale for targeting ROCK2 in IPF

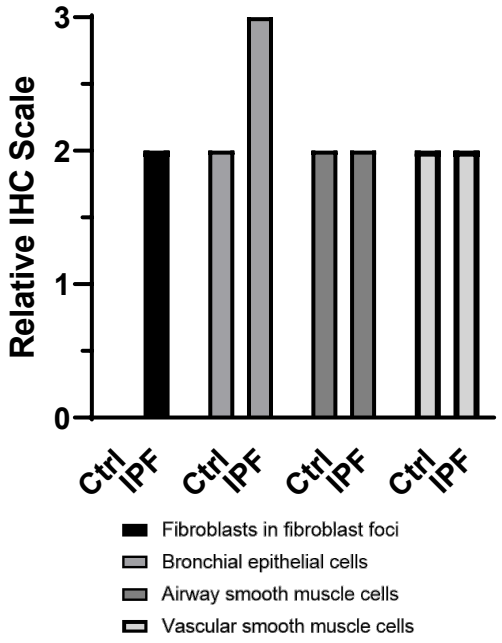
RhoA/ROCK/ROCK2 signalling pathway is enhanced in human IPF patients



(Myo)fibroblasts isolated from lungs of patients with IPF (n = 8), non-IPF control subjects (n = 6)
ROCK activity assays using a colorimetric approach. Data are mean ± SD

Adapted from Zhou2013

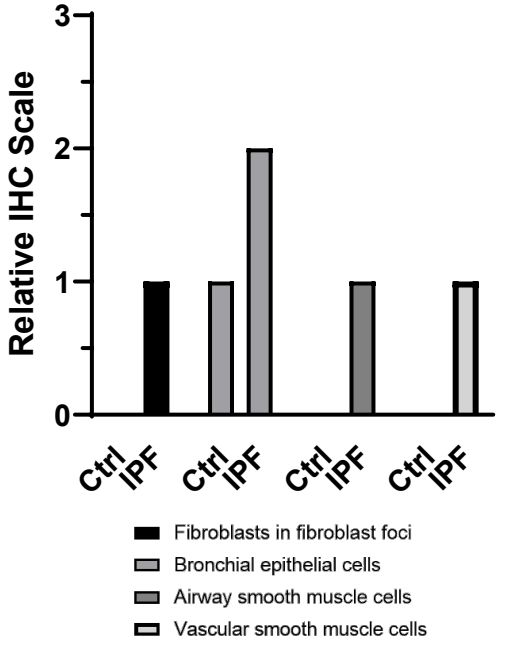
Strong increase of ROCK2 expression in IPF bronchial epithelial cells



Intensity of immunostaining evaluated on a scale of 0 to 3
N=6 per group; NF: not found

Adapted from Shimizu2014

Moderate increase of p-MYPT-1 expression in IPF bronchial epithelial cells



Intensity of immunostaining evaluated on a scale of 0 to 3
N=6 per group; NF: not found

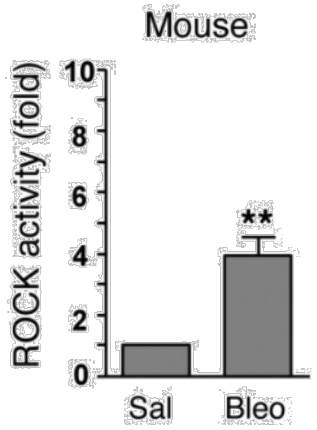
Adapted from Shimizu2014

IPF: Idiopathic pulmonary fibrosis; ROCK: Rho associated protein kinase

Reduction of Markers of Fibrosis & Fibrogenesis in the Murine Lung Bleomycin Model

Strong literature rationale for targeting ROCK2 in IPF

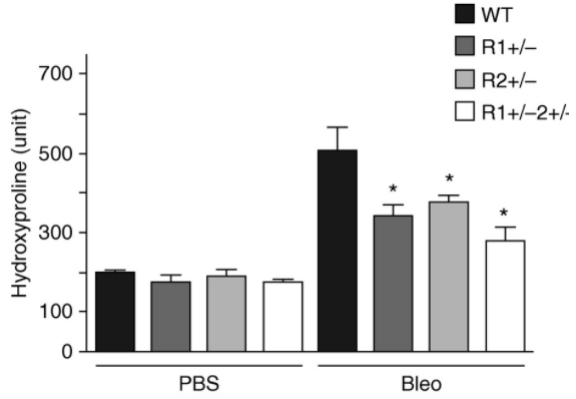
RhoA/ROCK/ROCK2 signalling pathway is enhanced in bleomycin-induced mice



(Myo)fibroblasts isolated from lungs of bleomycin-treated mice (n = 8), and saline-treated mice (n = 8)
ROCK activity assays using a colorimetric approach. Data are mean ± SD

Adapted from Zhou2013

ROCK2+/- knockout mice are protected from bleomycin-induced pulmonary fibrosis

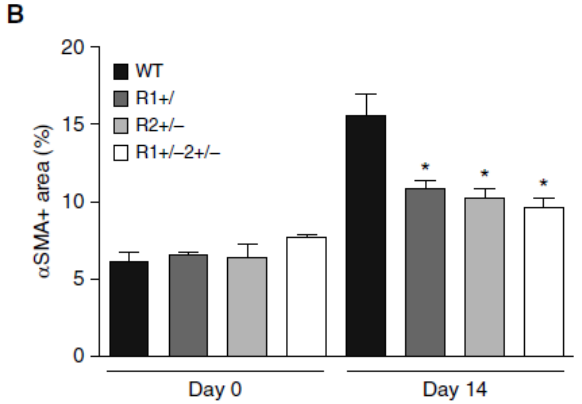


Genetic reduction in either or both ROCK isoforms affords protection from bleomycin-induced pulmonary fibrosis

Significant reduction in hydroxyproline content (lung collagen)

Adapted from Knipe2018

Both ROCK isoforms contribute to fibroblast activation induced by bleomycin injury



Significant reduction in α-SMA staining at Day 14 post-bleomycin

Adapted from Knipe2018

IPF: Idiopathic pulmonary fibrosis; ROCK: Rho associated protein kinase

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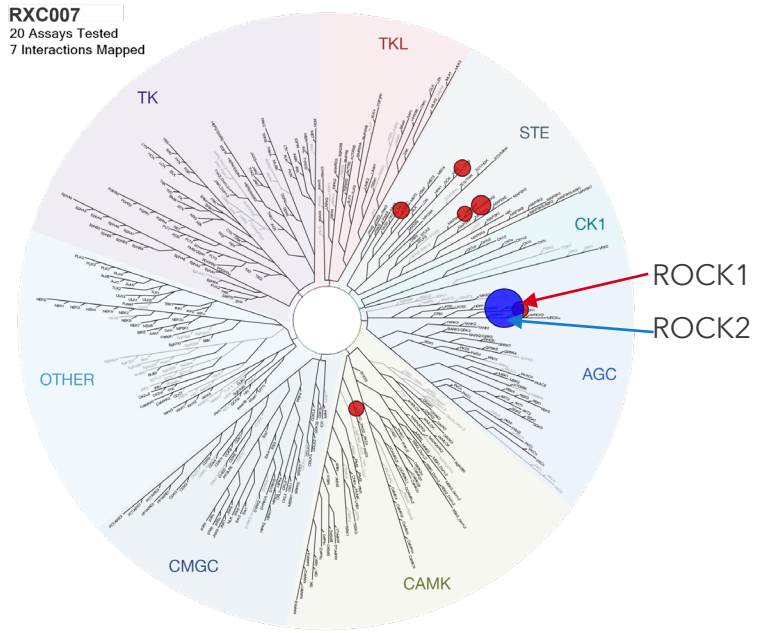
RXC007 – A Highly Specific ROCK2 Selective Inhibitor to Tackle IPF and Fibrotic Disease

RXC007 is a Highly Selective ROCK2 Inhibitor

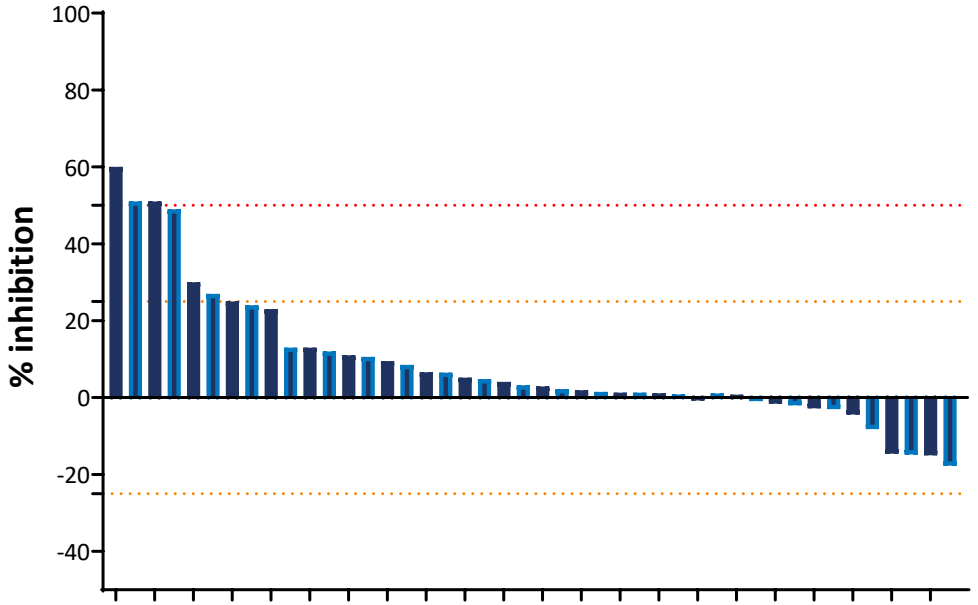
Highly selective when tested in 468-kinase panel (IC_{50} follow-up) and against 44 enzymes (% inhibition at 10 µM)

KinomeScan kinase panel



- Kinases with IC_{50} values < 3 µM assayed at Km [ATP] marked with circles
- ROCK2, the most potently inhibited kinase, is denoted with a blue circle
- RXC007 is >100x selective for ROCK2 over ROCK1

CEREP (SafetyScreen44TM)

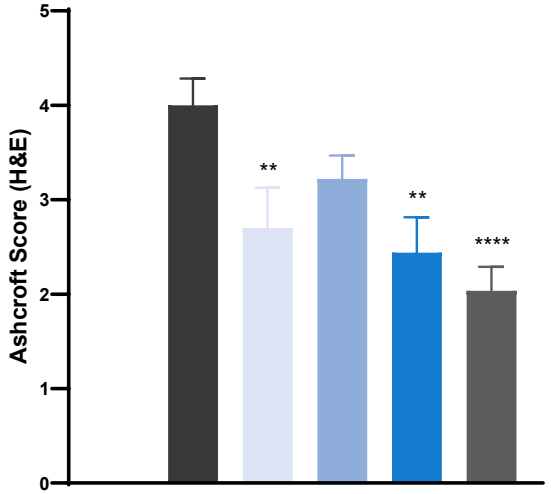


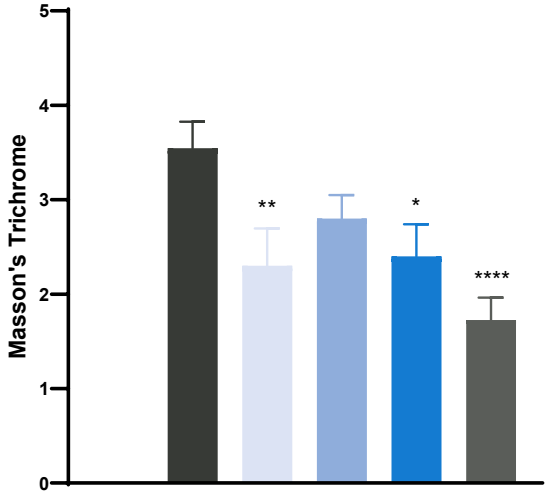
- 3 enzymes showing an inhibition or stimulation higher than 50% (Total of 7 targets inhibited with more than 25%)
- PDE3A: 60%; 5-HT transporter (antagonist) 51%; dopamine transporter (antagonist): 51%
  - Follow up IC_{50}: PDE3A IC_{50} 23 µM

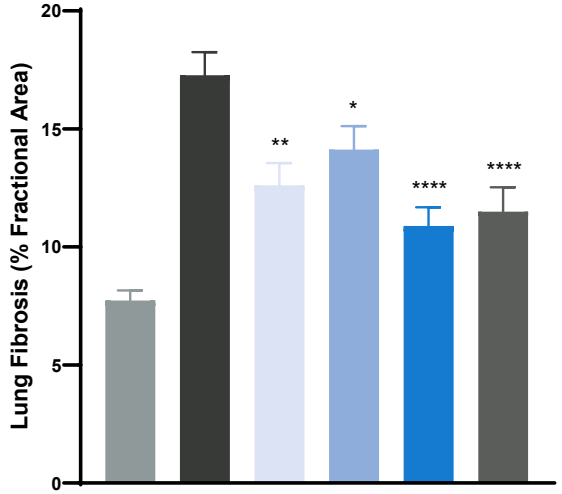
ROCK: Rho associated protein kinase

RXC007 Reduces Fibrosis and Collagen Deposition in a Therapeutic Murine Bleomycin-induced Lung Fibrosis Model

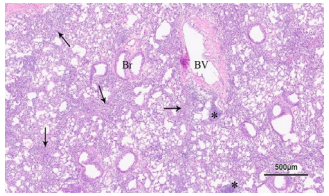
21-Day therapeutic murine bleomycin-induced lung fibrosis model (dosing from day 7)



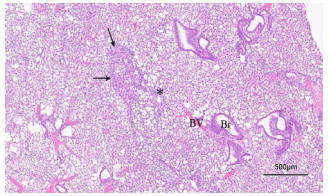




Vehicle

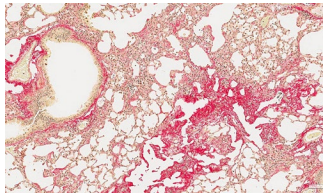


RXC007 50 mg/kg BID



- Vehicle
- Bleomycin Vehicle
- RXC007 (5 mg/kg BID)
- RXC007 (20 mg/kg BID)
- RXC007 (50 mg/kg BID)
- Pirfenidone (100 mg/kg BID)

Vehicle



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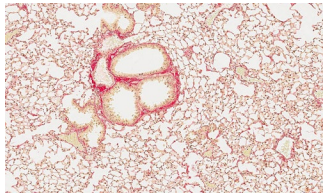
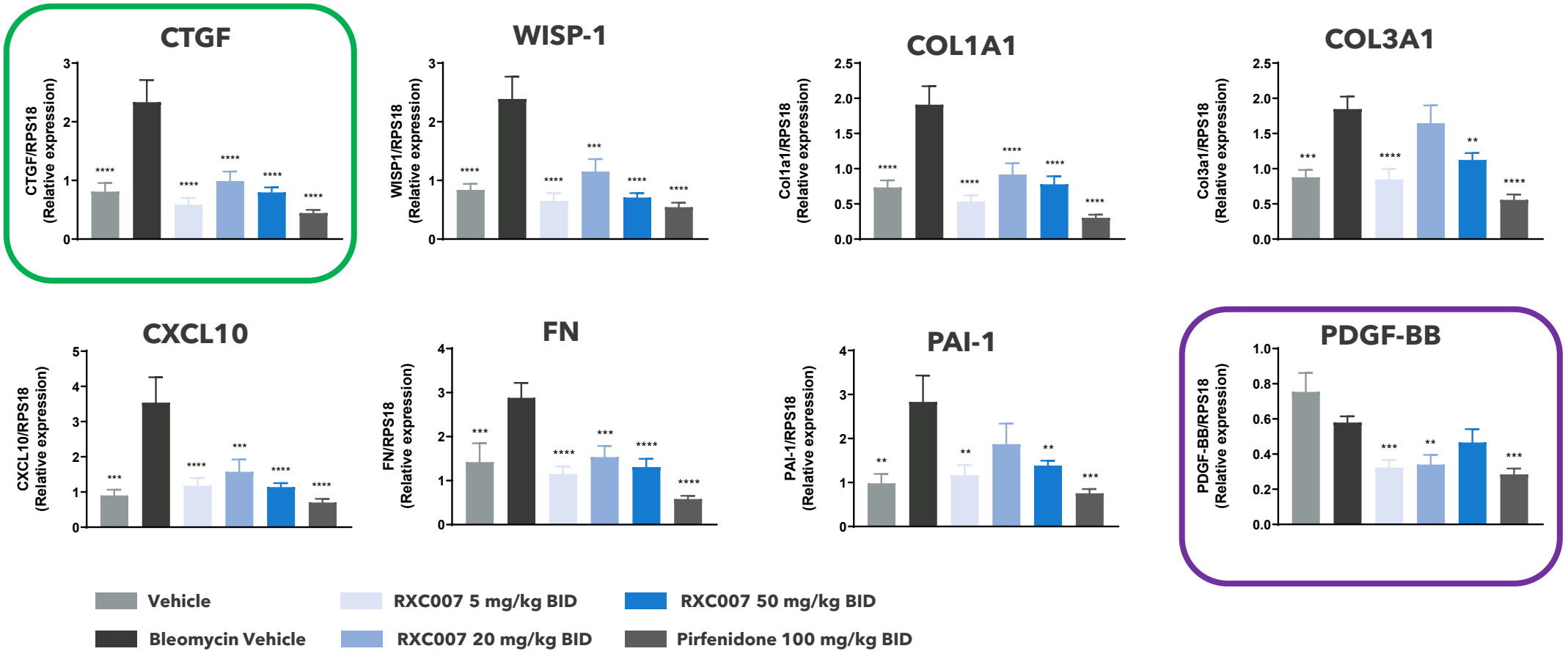


Note: Different vehicle used for pirfenidone. Only used as positive control.

BID: Twice daily

RXC007 Suppresses the Expression of a Number of Genes Strongly Associated with Fibrosis and Known Pro-fibrotic Drivers in IPF

21-Day therapeutic murine bleomycin-induced lung fibrosis model (dosing from day 7)



Green: Specific to Pamrevlumab
Purple: Specific to Nintedanib

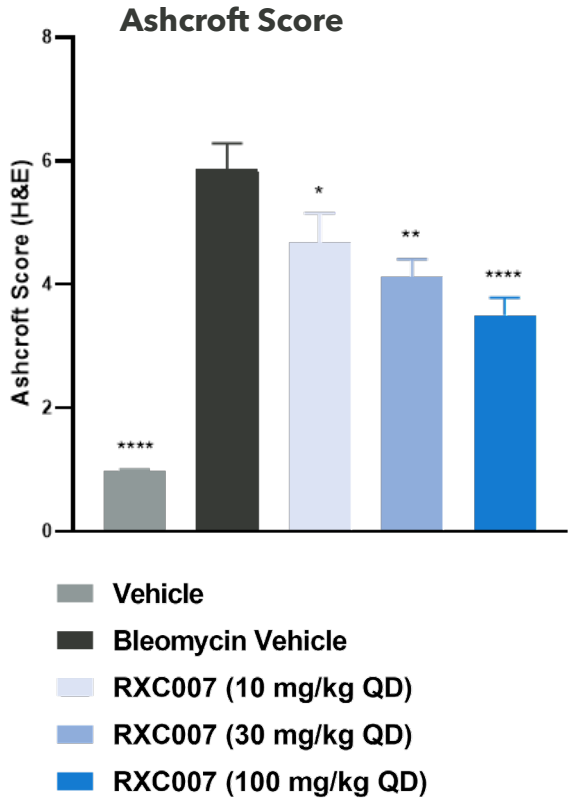
Note: Different vehicle used for pirfenidone. Only used as positive control.

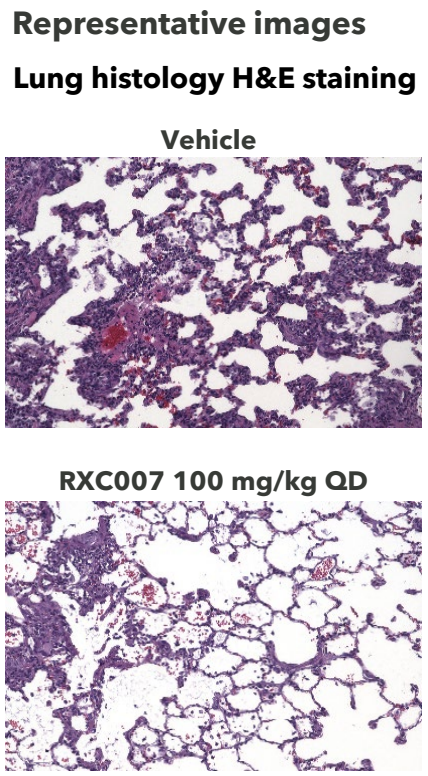
BID: Twice daily; IPF: Idiopathic pulmonary fibrosis

RXC007 Reduces Fibrosis and Collagen Deposition in Rat Bleomycin-induced Lung Fibrosis Models

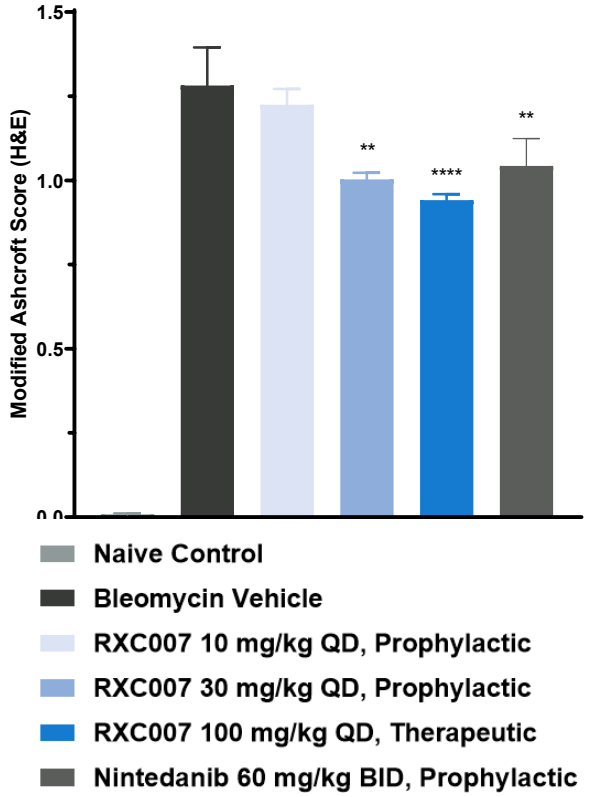
RXC007 is efficacious in rat bleomycin-induced IPF models

10-Day prophylactic rat BLM-induced lung fibrosis model (dosing from day 1)





28-Day prophylactic & therapeutic rat BLM-induced lung fibrosis model (dosing from day 1 or 7)



Note: Different vehicle used for nintedanib. Only used as positive control.

BID: Twice daily; IPF: Idiopathic pulmonary fibrosis; QD: Once daily

RXC007 Modulates Pro-fibrotic Gene and Protein Expression in Human IPF *Ex-vivo* Lung Tissue

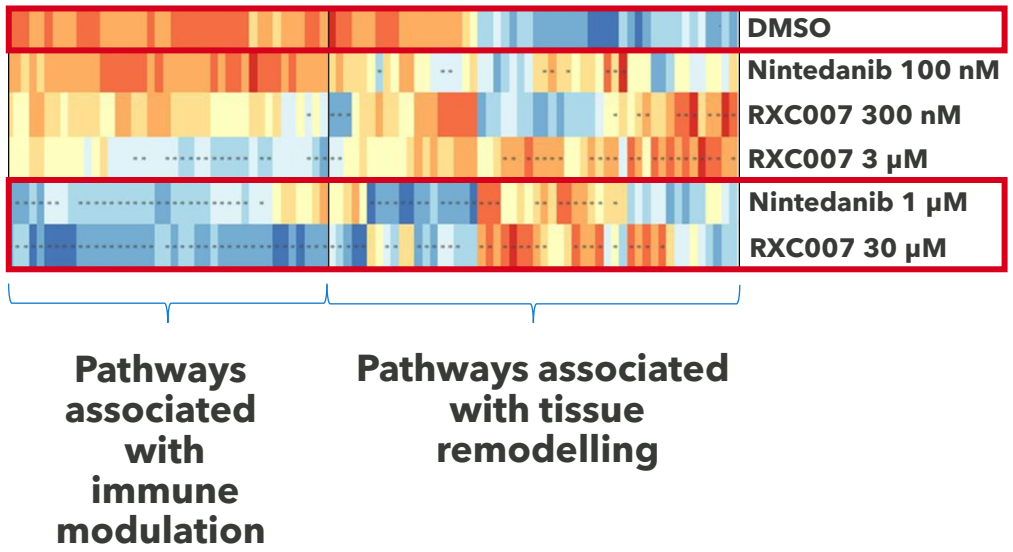
Modulation of fibrotic gene & protein expression in IPF tissue

Gene expression heatmap

Gene pathways expression

Low ◄ ► High

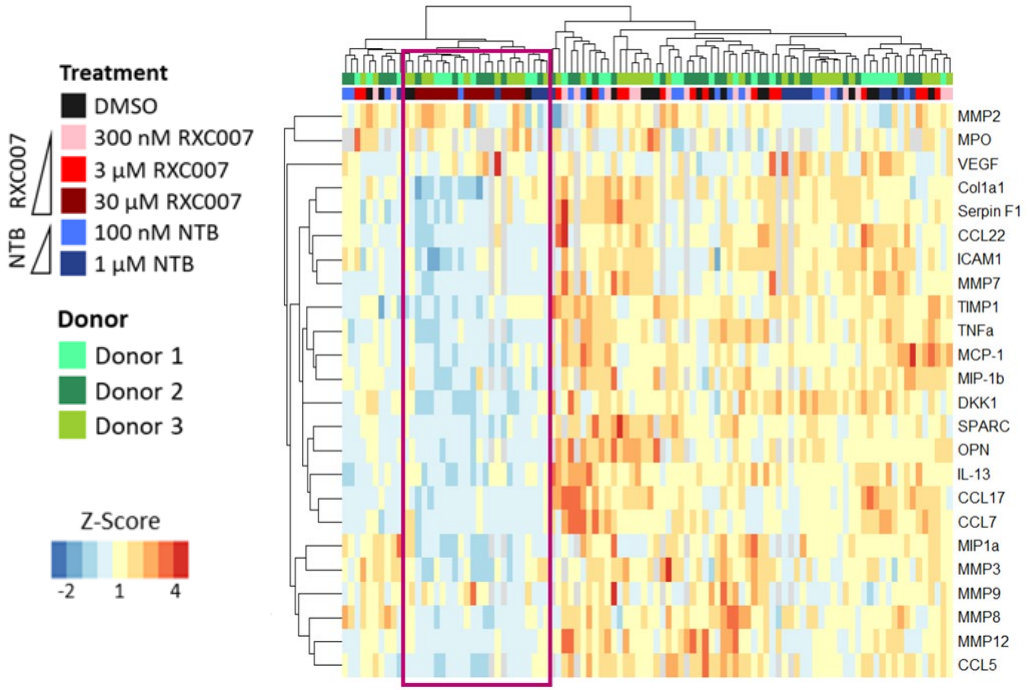
* Significant changes



Protein expression heatmap

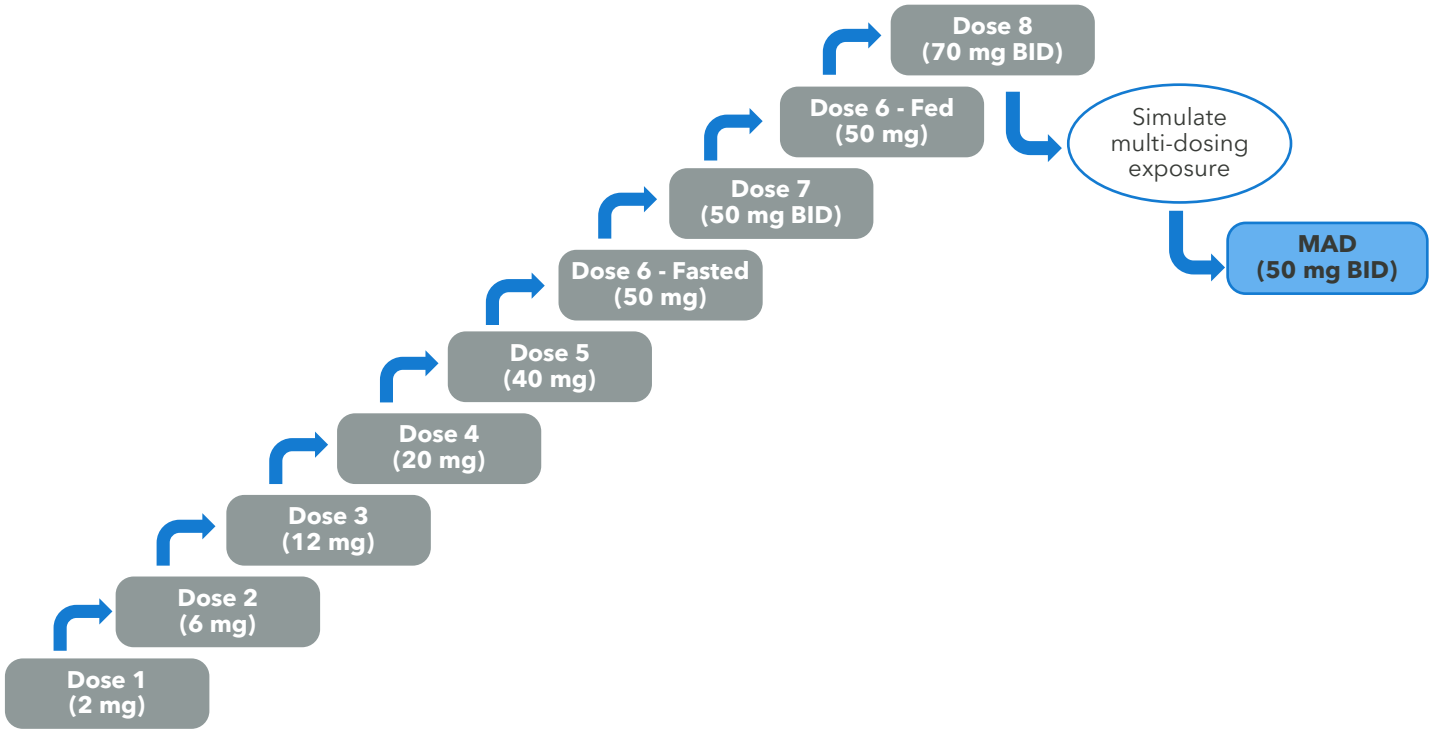
Pro-fibrotic proteins measured in supernatant

30 µM RXC007 – Downregulation*



IPF: Idiopathic pulmonary fibrosis

RXC007/0001: A Randomised, Double-blind, Placebo-controlled, Single-ascending Dose and Multiple dose, First-in-human, Phase 1

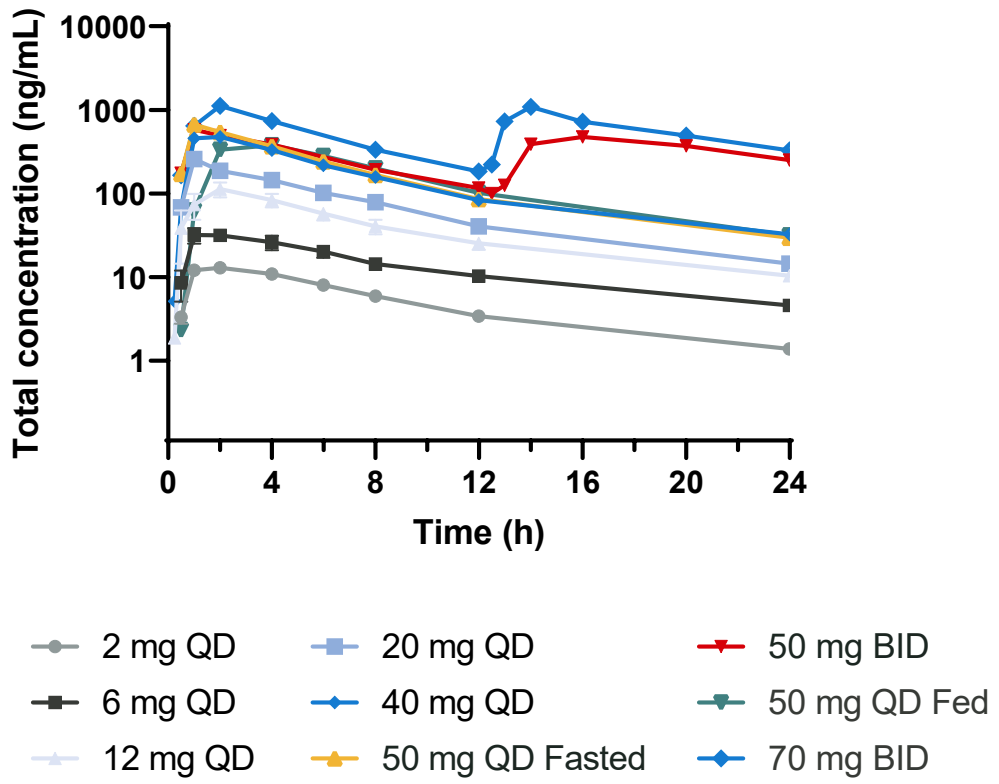


Part 1 (SAD)	**Dose escalation cohorts:** Double-blind, placebo-controlled, to assess the safety and tolerability of RXC007 in healthy subject cohorts following single dose
Part 2 (MAD)	**Dose expansion cohort:** Double-blind, placebo-controlled, to assess the safety and tolerability of RXC007 monotherapy in healthy subjects following 14-28 days of daily dosing

BID: Twice daily; MAD: Multiple ascending dose; PK: Pharmacokinetic; QD: Once daily; SAD: Single ascending dose

Excellent Safety and Pharmacokinetic Profile in SAD Phase 1 in Healthy Volunteers

Total plasma concentration over time



Excellent safety and pharmacokinetic profile

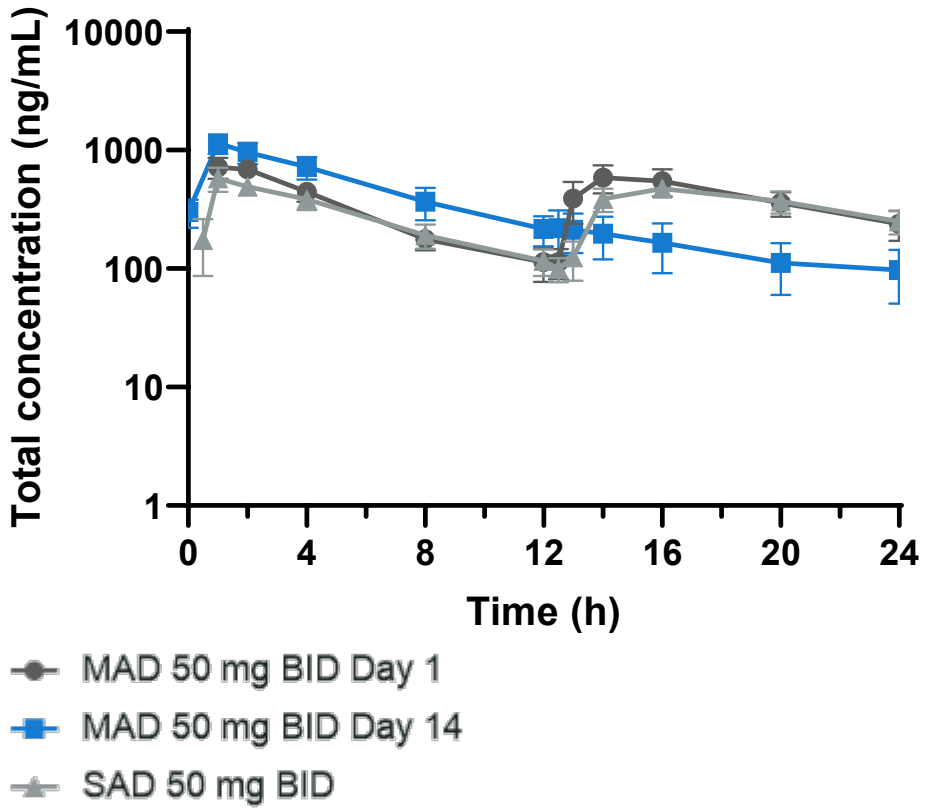
- Pharmacokinetics as predicted from preclinical data
  - Following single-dose administration of oral RXC007 capsule (2 mg QD to 70 mg BID) to healthy participants, plasma concentrations reached maximum levels after 1.25 to 1.8 hours.
  - Mean half-life remained relatively unchanged with increasing dose, ranging from 9.0 to 11 hours. Slightly lower for 2 mg dose (6.8 h)
  - Essentially linear exposure 2-70 mg
- No significant differences between 50 mg QD fasted and fed cohorts
- Single Ascending Dose (SAD) escalations completed
- No adverse events observed to date following single oral dose of 2 mg QD to 70 mg BID

BID: Twice daily; QD: Once daily; SAD: Single ascending dose

RXC007 was Safe and Well Tolerated in 50 mg BID Multi Dose Cohort with Few Treatment-emergent AEs (TEAEs) Reported

Preliminary data review 3 March 2022

Total plasma concentration over time



Safety

- No Serious Adverse Events (SAEs) were reported
- 2 subjects reported 6 Adverse Events
  - **Subject 1:** Malaise, Abdominal Discomfort, Headache (Intermittent), and Fatigue
  - **Subject 2:** Brief twitching muscle in chest, Brief left leg muscle twitching
  - All AEs were transient, mild and reversible, no dose changes required
- There were no notable changes in vital signs, ECGs, physical examination, or any clinical laboratory parameters

AE: Adverse events; BID: Twice daily; ECG: Electrochardiogram; MAD: Multiple ascending dose; QD: Once daily; SAD: Single ascending dose; SAE: Serious adverse events; TEAE: Treatment-emergent adverse events

Lead Indication is IPF with Phase 2 Start Expected 2022

Highlights

- ROCK is a validated compelling target at a key junction in cell signalling pathway central to fibrosis
- RXC007 is a highly potent, selective and orally active ROCK2 inhibitor
- Strong preclinical efficacy data supports clinical development plan in IPF
- To date* no clinically significant adverse events observed in Phase 1 healthy volunteers and observed PK profile in line with prediction from preclinical data
- Phase 1 SAD and 50 mg BID multi dose cohorts completed
- Plan to start a staged Phase 2 approach in 2022
- Initial 12-week Phase 2a study for early efficacy readouts, safety and tolerability in IPF patients +/- SoC, in addition to target and disease biomarker engagement
- Phase 2a dose-ranging study will inform Phase 2b dose
- Phase 2b will dose RXC007 over 12 months plus SoC with FVC lung function primary endpoint

*Interim data on 3 March 2022

FVC: Forced Vital Capacity; IPF: Idiopathic Pulmonary Fibrosis; PK: Pharmacokinetic; ROCK: Rho Kinase; SoC: Standard of care