Potential of RXC007, a highly selective Rho-Associated Coiled Kinase 2 (ROCK2) inhibitor, to tackle fibrotic lung disease
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Introduction

• ROCK is a member of the AGC family of serine/threonine kinases that are involved in many aspects of cellular signalling
• Rho/ROCK signalling closely involved in regulating cell morphology, growth, migration, and apoptosis
• Highly conserved in mammalian species, two subunits of ROCK are known to exist: ROCK1 and ROCK2
• Both ROCK1 and ROCK2 are involved in numerous profibrotic processes with pan-ROCK inhibitors able to strongly suppress TGFβ-stimulated myofibroblast activation, chemokine-driven fibroblast migration, and EMT in response to profibrotic mediators such as lysophosphatidic acid (LPA) and endothelin
• Systemic administration of pan-ROCK inhibitors induces vasodilation, hypotension, limiting their use as therapeutic agents but selective ROCK2 inhibition circumvents these side-effects

Rationale for ROCK2 Inhibition in Interstitial Lung Diseases and Idiopathic Pulmonary Fibrosis

• ROCK activity significantly increased in fibroblasts isolated from human IPF tissue and bleomycin-induced murine lung fibrosis

IHC analysis of ROCK2 expression in resected IPF lung tissue

• Increased ROCK2 expression is observed in airway or vascular smooth muscle cells

ROCK2 activity in mouse & human lung tissue

• ROCK activity in mouse lung tissue
• ROCK activity in human lung tissue

ROCK2 is insufficient to protect from bleomycin-induced lung fibrosis in mouse models

• Naphthylsulfonflic ROCK1, ROCK2 and ROCK2/ROCK2 mice show reduced hydroxyproline expression in bleomycin-induced lung fibrosis at day 14
• Similar reduction in mRNA expression in fibroblasts is observed in the 3 haploinsufficient phenotypes

Rationale for ROCK2 Inhibition

1. ROCK2 is a member of the AGC family of serine/threonine kinases that are involved in many aspects of cellular signalling.
2. Rho/ROCK signalling is closely involved in regulating cell morphology, growth, migration, and apoptosis.
3. Highly conserved in mammalian species, two subunits of ROCK are known to exist: ROCK1 and ROCK2.
4. Both ROCK1 and ROCK2 are involved in numerous profibrotic processes with pan-ROCK inhibitors able to strongly suppress TGFβ-stimulated myofibroblast activation, chemokine-driven fibroblast migration, and EMT in response to profibrotic mediators such as lysophosphatidic acid (LPA) and endothelin.
5. Systemic administration of pan-ROCK inhibitors induces vasodilation, hypotension, limiting their use as therapeutic agents but selective ROCK2 inhibition circumvents these side-effects.

Study Design of the Therapeutic Murine Bleomycin-induced Lung Fibrosis Model (14-day treatment)

A total of 65 male C57BL/6 mice from Taconic were included in this study. The animals were divided into 6 groups. Animals in groups 2, 3, 4, 5, and 6, were administrated 1.5 μg amounts of clinical bleomycin via oropharyngeal route. RXC007 and pirfenidone were dosed therapeutically from Day 7 to Day 21 via oral gavage.

ROXC007 reduces fibrosis and collagen deposition in a Therapeutic Murine Bleomycin-induced Lung Fibrosis Model

• RXC007 reduces fibrosis and collagen deposition in fibroblasts isolated from human IPF tissue and bleomycin-induced murine lung fibrosis.

ROXC007 suppresses the expression of a number of drivers strongly associated with fibrosis and in IPF

• RXC007 reduces cutaneous Pdgfra+pJnk1/2+ fibroblasts
• JNK signalling is known to be strongly upregulated in activated fibroblasts and associated with pro-inflammatory and pro-fibrotic gene expression.

Summary

• RXC007 is a highly potent, selective and orally-active ROCK2 inhibitor currently in Phase 2a in IPF.
• ROCK2 is a validated, compelling target at a key junction in cell signalling pathways central to fibrosis – IPF and CF-ILD.
• Robust preclinical efficacy data across disease models supports clinical development plan in lung fibrosis – IPF and CF-ILD.

References