Redx Pharma Plc, Alderley Park, Macclesfield, United Kingdom.

Redx Pharma

ROCK2 inhibitors for the treatment of fibrosis

Emily P. Offer, Nicolas E.S. Guisot, Stuart A. Best, Philip MacFaul, Sara Ceccarelli, Matthew R. Box, Neil Hawkins, Rosie Knowles, Rebecca Holland, Peter R. Bunyard, Clifford D. Jones, Richard Armer.

INTRODUCTION

- ROCK2 is central to disease processes driving fibrosis pathology
- ROCK2 acts on: αSMA, TGFβ, Col1a1, MMP-2, CTGF, IL-6, TNFα, Bcl2
- ROCK2 activity in vascular endothelium of diabetic mice
- ROCK2 inhibitors have been shown to decrease collagen deposition and fibrosis
- ROCK2 inhibitors reduce fibrosis in liver in vitro and in vivo
- ROCK2 inhibitors reduce fibrosis in diabetic mice
- ROCK2 inhibitors reduce fibrosis in fibroblast and lung fibroblast
- ROCK2 inhibitors reduce fibrosis in mouse, rat, dog, and human

RESULTS

- ROCK2 inhibitors reduce markers of fibrosis in human liver in vitro models
- ROCK2 inhibitors reduce primary human hepatic stellate cell activation and fibrogenic gene expression in vitro
- ROCK2 inhibitors reduce lipid accumulation in primary human hepatocytes in vitro

NOTE:
- ROCK2 and αSMA expression in the vascular endothelium is responsible for the control of vascular tone and systemic release of pro-ROCK inhibitors have been shown to induce a drop in arterial blood pressure leading to a corresponding increase in heart rate 
- ROCK2 inhibitors would not induce hypotension.

Redx's ROCK2 inhibitors are potent and highly selective
- Redx1058 and Redx10616 are potent and highly selective ROCK2 inhibitors.
- Cellular potency of ROCK2 selective inhibitors determined by measuring inhibition of αMYPT1, a substrate downstream of ROCK in M17 cell lines, ROCK1 or ROCK2 selective cell lines were generated with siRNA.

Redx10616 has suitable in vitro ADME properties and is orally bioavailable
- ROCK2 inhibitors are highly selective ROCK2 inhibitor across a panel of 422 kinases, and the in CEREF safety panel with no off-target activites observed
- Low to medium in vitro clearance and conserved across species (mouse, rat, dog, and human)

Redx10616 has suitable in vitro ADME properties and is orally bioavailable
- Inhibition of pMYPT1 in parental and ROCK1 or ROCK2 knockdown cell protected from bleomycin induced lung injury
- ROCK2 inhibitors for the treatment of fibrosis
- ROCK2 inhibitors reduce markers of fibrosis in human liver in vitro models
- ROCK2 inhibitors reduce primary human hepatic stellate cell activation and fibrogenic gene expression in vitro
- ROCK2 inhibitors reduce lipid accumulation in primary human hepatocytes in vitro

Summary

- Redx has developed a series of compounds that are potent ROCK2 inhibitors in biochemical & cellular in vitro assays.
- These compounds are highly selective against ROCK1 and a panel of kinases.
- Targeting ROCK2 selectively allows a safe cardiovascular profile, as previously demonstrated in telemetry rats.
- Demonstration that physiologically relevant markers of fibrosis pathways can be modulated in vivo with a selective ROCK2 inhibitor.
- No safety concerns highlighted from early in vitro assessment (iVES, CEREF).
- This encouraging profile of tool compound REDX10616 is representative of the potential of the chemical series which are currently in lead optimisation.
- In vivo studies with ROCK2 selective inhibitors in NASH STAM, UUG kidney and IF animal models of fibrosis are ongoing.