INTRODUCTION

ROCK2 is central to disease processes driving fibrosis pathology.

ROCK2 in vitro and in vivo

ROCK2 inhibitors reduce fibrosis markers in kidney models in vitro and in vivo

A: ROCK2 selective compounds inhibit in vitro expression of fibrosis markers in kidney mesangial cells

1. Mesangial cells cultured in high glucose for 9 days; model diabetic environment (compounds day 4-9).
2. Protein expression of CTGF, fibronectin, PGDF-BB, TIMP-1 and MCP-1 detected in the culture media.

B: ROCK2 inhibitor reduces inflammatory response in vivo, in model of acute kidney injury

1. Cisplatin induces an acute inflammatory response and fibrosis in the kidney.
2. ROCK2 inhibitor expression reduces the inflammatory response.

C: ROCK2 selective inhibitors REDX10843 and REDX1616 reduce the expression of genes associated with inflammation and fibrosis.

ROCK2 inhibitors reduce fibrosis markers in liver models in vitro and in vivo

A: ROCK2 selective compounds reverse myofibroblast phenotype in HSC derived myofibroblasts

1. Hepatic stellate cell line differentiated on stiff plastic for 2 weeks demonstrate myofibroblast morphology and phenotype by induction of αSMA protein expression.
2. Induction of αSMA with ROCK2 inhibitors indicates suppression of the myofibroblast phenotype.

B: ROCK2 inhibitors reduce fibrosis markers in the STAM NASH model

1. Selective ROCK2 inhibitor REDX10843 dosed therapeutically in the murine STAM NASH model significantly reduces fibrosis in the liver when dosed 80 or 100 mg/kg.

SUMMARY

- Redx have developed a series of compounds that are potent ROCK2 inhibitors in biochemical & cellular in vitro assays and highly selective against ROCK1 and a panel of kinases.
- No safety concerns highlighted from early in vitro assessment (HERG, CERP, AMES, micronucleus).
- ROCK2 inhibition modulates fibrotic parameters with ROCK2 selective inhibitors demonstrating in vivo activity.
- Targeting ROCK2 selectively allows a safe cardiovascular profile, as previously demonstrated with REDX10178 in telemetered rats.
- The encouraging profile of series compounds is representative of the potential of the chemical series which are currently in lead optimisation.
- ROCK2 inhibition modulates fibrotic parameters in vivo with REDX10843, selective ROCK2 inhibitor.