**ROCK2 inhibitors for the treatment of NASH**

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**INTRODUCTION**

ROCK2 is central to disease processes driving fibrosis pathology

- ROCK2+/- on HFD protected against loss of insulin sensitivity, & prolonged survival from heart dysfunction.
- ROCK2 activity in vascular endothelium of DIO/obesity animals.
- ROCK2 knockdown reduced albuminuria, TGFβ, fibrosis & vascular dysfunction.
- ROCK2+/- had improved morphological parameters of diabetes induced hypertension.

- ROCK2 inhibition in liver of dietary & diet-induced liver fibrosis.
- ROCK2 silencing drives activation of hepatic stellate cells & fibrosis.

**RESULTS**

**ROCK2 inhibitors reduce markers of fibrosis in human liver in vitro models**

- RedX ROCK2 inhibitors reduce primary human hepatic stellate cell activation and and fibrogenic gene expression in vitro.

- RedX ROCK2 inhibitors reduce lipid accumulation in primary human hepatocytes in vitro.

**ROCK2 inhibitors reduce markers of fibrosis in human liver in vivo models**

- RedX ROCK2 inhibitors reduce primary human hepatic stellate cell activation and and fibrogenic gene expression in vivo.

**SUMMARY**

- Redx have developed a series of compounds that are potent ROCK2 inhibitors in biochemical & cellular in vitro assays.
- These compounds are highly selective against ROCK2 and a panel of kinases.
- Targeting ROCK2 selectively allows a safe cardiovascular profile, as previously demonstrated in telemedicated rats.
- Selective ROCK2 inhibitors reverse fibrogenic phenotype of activated human hepatic stellate cell fibroblasts and fibrosis.

- Demonstration that physiologically relevant markers of fibrosis pathways can be modulated in vivo with selective ROCK2 inhibitors.
- No safety concerns highlighted from early in vitro assessment (H&E, CERRP).
- Redx’s highly selective ROCK2 lead compound shows robust preclinical in vivo efficacy in murine liver, kidney and lung fibrosis models (undisclosed data).

**Redx’s ROCK2 inhibitors are potent and highly selective**

- RedX10178 and RedX10616 are potent and highly selective ROCK2 inhibitors.

- Cellular potency of ROCK2 selective inhibitors is determined by measuring inhibition of pMYPT1, a substrate downstream of ROCK2, in MC7 cell lines; ROCK2 or ROCK2 selective cell lines were generated with SHMA.

**ROCK2 inhibitors prevent the release of pro-inflammatory and pro-fibrotic factors in kidney mesangial cells grown in high glucose**

- Protein expression of CTGF, fibronectin, PDGF-BB, TIMP-1, MMP-2 and MCP-1 detected in the culture media.

**RedX10178 and RedX10616 suppress inflammatory, fibrosis and kidney injury pathways in a model of acute kidney injury**

- Mice treated for 5 days with compound orally, OD or BD. Single IP injection of capstatin on day 3 indicates an acute inflammatory infiltrate.
- This inflammation and injury response in the kidney leads to an increase in the expression of ROCK2 but not ROCK1.
- RedX10178 and RedX10616 modify the expression of genes associated with inflammation, fibrosis and kidney injury in a dose dependent manner.

**Pro-inflammatory and pro-fibrogenic gene expression change following RedX10178 treatment (BD)**

**Pro-inflammatory and pro-fibrogenic gene expression change following RedX10616 treatment (QD)**

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