Intestinal fibrosis associated with Inflammatory Bowel Disease (IBD) is a significant issue.

- In the U.S. 30-40% patients have stricturing and obstruction to bowel wall fibrosis within 10 years of diagnosis of inflammatory bowel disease (IBD).
- Surgical resections to remove fibrostenosis are required in 80% of cases but recurrence rates are up to 70%.
- Treatment with biologics has resulted in only a small decrease in the rate of surgical interventions.
- Even in the absence of inflammation, tissue damage and fibrosis continue to progress with increased accumulation and crosslinking of extracellular matrix (ECM).
- Preventing or reversing ECM deposition in IBD is a major therapeutic challenge.

**Key pathways in fibrosis**

- The transition of quiescent mucosal fibroblasts into activated myofibroblasts occurs via multiple stimuli such as TGFβ, IL6 and mechanical stimuli (matrix stiffness).
- Activated myofibroblasts produce ECM components such as collagen and remodelling enzymes e.g. matrix metalloproteinases (MMPs) and pro-fibrotic cytokines including TGFβ and IL6.
- Myofibroblasts formed by epithelial to mesenchymal transition (EMT) of epithelial cells into myofibroblasts are also a source of effector cells contributing to fibrosis.

**ROCK is involved in multiple aspects of fibrosis**

- ROCK (Rho-associated coiled-coil containing protein kinase) is a serine/threonine protein kinase with two ubiquitously expressed isoforms, ROCK1 and ROCK2.
- ROCK activation leads to the formation of stress fibres through actin polymerisation, this results in the release of myocardin-related transcription factors (MRTFs) that translocate to the nucleus and activate genes involved in cell differentiation and cytoskeletal organisation.
- The involvement of ROCKs in myofibroblast activation, cytoskeletal organization, EMT and autophagy has highlighted their potential for anti-fibrotic therapy.

**GI restricted ROCK inhibitors could avoid the toxicity of systemic ROCK inhibition**

- The therapeutic potential of systemic ROCK inhibitors have been limited due to the target-related smooth muscle relaxation of systemic vasculature leading to hypotension.
- Local delivery of a potent ROCK1/2 inhibitor to the intestinal lumen could avoid the issues associated with systemic exposure.
- REDX08087 is a potent and pan-kinase selective ROCK1/2 inhibitor with suitable properties for local delivery to the GI mucosa.
- REDX08087 reaches high local GI concentrations but with limited systemic exposure due to rapid degradation in plasma.

**GI restricted ROCK inhibitors have limited systemic exposure**

- Limited systemic exposure in rat pharmacokinetic (PK) studies at doses significantly above therapeutic levels.
- Significant drug concentrations remain in colon tissue, even 24hr after dosing.

**GI restricted ROCK inhibitors can reverse a fibrotic phenotype in human intestinal fibroblasts**

- Significant suppression of the number of activated fibroblasts expressing α-SMA after intermittent treatment with REDX08397.
- Suggests that ROCK inhibition can induce reversal of the pro-fibrotic myofibroblast phenotype.

**Gi restricted ROCK inhibitors in an adoptive T-cell transfer model of IBD but do not impact on inflammation**

- Anti-TNF treatment improves inflammation scores and decreases the production of inflammatory markers IFNγ, MCP1, IL6 and IL1β but has no effect on fibrosis.
- In contrast, REDX08087 monotherapy has no effect on inflammation score but a reduction in histological fibrosis and the production of TGFβ and IL6 were observed.
- Combination of REDX08087 and anti-TNF results in reduction of fibrosis to control levels.

**GI restricted ROCK inhibitors can reverse established fibrosis in a chronic DSS model of inflammatory bowel disease**

- Fibrosis established in mice by treatment with 2 cycles of DSS, then subsequent treatment with REDX08087 for 3 or 6 weeks at either 3 or 10mg/kg QD.
- Treatment with REDX08087 10mg/kg QD significantly reduced both the amount of fibrotic tissue and α-SMA protein density.
- 3 or 6 weeks treatment with 10 mg/kg REDX08087 also significantly reduced colonic levels of IL6, TGF-β1, and MMP-2, -8, -9, -12.

**Conclusions**

- REDX GI restricted ROCK inhibitors can potentially suppress TGFβ activation of fibroblasts.
- REDX GI restricted ROCK inhibitors also show the ability to suppress α-SMA in TGFβ activated human intestinal fibroblasts.
- Fibrosis can be prevented from developing in an adoptive T-cell transfer model of inflammatory bowel disease.
- Established fibrosis can be reversed in a DSS induced model of inflammatory bowel disease.
- Further studies are ongoing to assess the therapeutic potential of GI restricted ROCK inhibitors to reduce stenosis formation in IBD.

**References**