Pathway Suppression and Fibrosis

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**BACKGROUND**

- Wnt signalling is known to be important for tissue remodelling in several pathologies including cancer, auto-immunity and fibrosis.
- Porcupine (PORCN) is a membrane-bound O-acyltransferase required for and dedicated to palmitoylation of Wnt ligands, an essential step in the processing of Wnt ligands for secretion.
- Inhibition of Wnt signalling is likely to impact on several mechanisms that underlie tissue remodelling in fibrotic diseases such as suppression of inflammation, reduction of apoptosis, prevention of epithelial mesenchymal transition and inhibition of fibroblast activation.

**RESULTS**

**RXC006 displays favourable properties in vitro and in vivo ADME assays**

- *In vitro* metabolic stability, permeability and free fraction are superior to oral administration. *In vivo* data across preclinical species show good bioavailability and exposure (data not shown).

**RXC006 demonstrates efficacy when dosed therapeutically in the UUO model**

- RXC006-dosed therapeutically in the UUO model of kidney fibrosis demonstrated significant anti-fibrotic effects.
- Fibrosis suppression was confirmed by collagen content in kidney tissue (data not shown).
- Pathway engagement was demonstrated via the suppression of fibroblast activation.

**RXC006 suppresses fibrosis therapeutically in the lung bleomycin model**

- Porcupine inhibitors RXC006 and RXC004 dosed therapeutically demonstrated significant anti-fibrotic effects in the murine bleomycin lung fibrosis model.
- Compounds caused significant reductions in lung weight, collagen deposition and reduction in pro-fibrotic genes - as exemplified by CTGF. Aten-2 and TGFβ gene expression were also reduced (data not shown).

**SUMMARY**

- Redx porcupine inhibitor RXC006 is a potent suppressor of both canonical and non-canonical signalling pathways.
- RXC006 can potently suppress the release of Wnt3a from L-Wnt3a cells and Wnt3a on lung fibroblasts leading to an intracellular accumulation of Wnt3a.
- RXC006 can potently suppress the release of Wnt5a from HLFs leading to an intracellular accumulation of Wnt5a.
- RXC006 displays favourable properties in vitro and in vivo ADME assays.
- RXC006 suppresses fibrosis therapeutically in the lung bleomycin model.
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