Porcupine inhibitors demonstrate suitability for use as novel anti-fibrotic therapeutics

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BACKGROUND

- Wnt signalling is known to be important for tissue remodelling in several pathologies including cancer, autoimmunity and fibrosis.1,2
- Porcupine (PORCN) is a membrane-bound O-acetyltransferase required for and dedicated to palmitoylation of Wnt ligands, an essential step in the processing of Wnt ligands for secretion.3
- Several recent publications have shown that PORCN inhibitors (PORCNi) can ameliorate fibrosis in a number of models of fibrosis including renal, heart, lung and skin.
- Inhibition of Wnt signalling is likely to impact on several mechanisms that underpin tissue remodelling in fibrotic diseases such as suppression of inflammation, reduction of apoptosis, prevention of epithelial mesenchymal transition and inhibition of fibroblast activation.4

RESULTS

PORCNi display potent Wnt pathway inhibition in Wnt reporter assay and anti-proliferative activity in a pancreatic cancer cell line

In vitro cellular assays demonstrate inhibition of the Wnt signalling pathway with RedxPORCNi.

<table>
<thead>
<tr>
<th>PORCNi</th>
<th>A: Wnt reporter assay IC50 (nM)</th>
<th>B: HPAF-II C50 proliferation assay (nM)</th>
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<tbody>
<tr>
<td>RCC004</td>
<td>0.09</td>
<td>1.60</td>
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<tr>
<td>REDX6109</td>
<td>0.44</td>
<td>0.79</td>
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<tr>
<td>C59</td>
<td>0.62</td>
<td>nd</td>
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REDX6109 displays favourable properties in vitro and in vivoADME assays

REDX6109 and CB1226 mouse PK (bol, 3mg/kg, i.p.)

Free drug and metabolites profiles (Porcon/Wnt reporter IC50)

- LogP: 2.9 NT
- Oral bioavailability: 85% (oral administration)
- Half-life: 125 minutes

In vitro metabolic stability, permeability and free fraction are supportive of oral administration. PK data across preclinical species show good bioavailability and exposure (data not shown).

PORCNi demonstrates efficacy when dosed therapeutically in the unilateral ureteral obstruction (UOO) model

In 2016, Malan et al. reported that C59 demonstrated suppression of tubular damage and fibrosis in a murine model of fibrosis. C59 was dosed prophylactically at 35mg/kg QD for 7 days. RedxPharma sought to replicate these effects with aPORCNi dosed therapeutically.

A. Sirius Red staining

Vehicle

REDX6109

B. RT PCR

AXIN-2

CTGF

Col1α1

Fibronectin

PORCNi is efficacious in UUO model of kidney fibrosis

AXIN-2/Col1α1 levels at 4 weeks were subject to unpaired t-test for 11 days. Vehicle Karboynmetylcellulose (0.1% Tween80) or REDX6109 (3mg/kg QD) were dosed from day 5 to 11 before the animals were sacrificed. A: Collagen deposition in the kidney was measured by Sirus Red staining (representative images). The percentage area of positive staining was assessed by double blind analysis (mean data n=1). B: RT PCR was performed on kidney tissue samples to show the effect of REDX6109 on markers of pathway activation (AXIN-2) and fibrosis (connective tissue growth factor (CTGF), type 1 collagen (Col1α1) and fibronectin). Genes of interest were normalised to GAPDH. Significant effects of treatment **p<0.01, ***p<0.001.

SUMMARY

- RedxPORCNi exhibit potent suppression of the Wnt signalling pathway and are able to suppress tumour cell proliferation. REDX6109 has been nominated as a CD for oncology indications.
- REDX6109 demonstrates a robust anti-fibrotic response when dosed therapeutically in a murine model of interstitial fibrosis.
- Suppression of fibrosis is achieved at in vivo concentrations that will have minimal impact on gastrointestinal Wnt related pathways.
- Preliminary data show Wnt signalling is a potent inhibitor of HLF proliferation and is likely to synergise with other profibrotic mediators to induce an aggressive fibrotic response to tissue injury.
- REDX6109 has been nominated as a candidate for development and CTA enabling studies have been successfully completed with First Time in Humans studies expected to begin mid-2017.

REFERENCES


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