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.1-3
• Porcupine (PORCN) is a membrane-bound O-linked glycosyltransferase required for and dedicated to palmitoylation of Wnt ligands, an essential step in the processing of Wnt ligands for secretion.2
• 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.1-3
• 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.1-3

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 Redx PORCNi.

<table>
<thead>
<tr>
<th>PORCNi</th>
<th>A: Wnt reporter gene activity IC50 (nM)</th>
<th>B: HPAF-II CS6 proliferation assay (nM)</th>
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<tbody>
<tr>
<td>RXCO04</td>
<td>0.90</td>
<td>1.60</td>
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<tr>
<td>RXD606109</td>
<td>0.44</td>
<td>0.79</td>
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<tr>
<td>C99</td>
<td>0.62</td>
<td>n.d</td>
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A. Wnt reporter assay

B. HPAF-II proliferation assay

PORCNi inhibit Wnt secretion. Donor cells secreting Wnt6a were treated with the Redx Pharma PORCNi RXD606109, RXCO04 or the PORCNi tool compound C99. Inhibition of Wnt6a secretion was detected via the transfer of conditioned media (CM), collected from donor cells, onto a β-catenin reporter cell line.

PORCNi demonstrate efficacy when dosed therapeutically in the unilateral ureteral obstruction (UUO) model

In 2016, Malian et al. reported that C99 demonstrated suppression of tubular damage and fibrosis in a murine model of fibrosis. C99 was dosed prophylactically at 35mg/kg QD for 17 days. Redx Pharma sought to replicate these effects with a PORCNi dosed therapeutically.

A. Sirius Red staining

B. RT PCR

PORCNIis efficacious in UUO model of kidney fibrosis.

Redx/Genentech aged 8-12 weeks were subject to unilateral ligation for 11 days. Vehicle treated mice (REDX606109-treated tissues above and standardised to a DMDS control (graphs right). Cell count at 80 was removed as baseline.

Summary

• Redx/PORCNi exhibit potent suppression of the Wnt signalling pathway and are able to suppress tumour cell proliferation. RXCO04 has been nominated as a CD for oncology indications.
• RXD606109 demonstrates a robust anti-fibrotic response when dosed therapeutically in a murine model of interstitial fibrosis.
• Suppression of fibrosis is achieved in vivo concentrations that will have minimal impact on gastrointestinal Wnt related pathologies.
• Preliminary data show Vantiglucin is a potent inhibitor of HIF signalling and is likely to synergise with other pro-fibrotic mediators to induce an aggressive fibrotic response to tissue injury.
• RXCO04 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: