**BACKGROUND**

- Wnt signalling initiates key oncogenic pathways in cancer. Wnt signalling pathways are implicated in tumour initiation, growth, senescence, cell death, differentiation and metastasis.¹
- Targeting the Wnt pathway is an attractive therapeutic approach to cancer treatment. Porcine (PORCIN) is a membrane-bound ß-acetyltransferase (MBAT) required for and dedicated to palmitoylation of Wnt ligands, an essential step in the processing of Wnt ligands for secretion.²
- There is a growing body of literature suggesting that the Wnt pathway plays a role in the host immune response to tumours and that activation of the pathway may result in resistance to checkpoint inhibitors.³ A PORCIN inhibitor has the potential to benefit patients with cancers in which Wnt signalling is implicated.⁴

**RESULTS**

**RXC004 displays potent Wnt pathway inhibitory activity and anti-proliferative activity in pancreatic cancer cell lines.**

<table>
<thead>
<tr>
<th>Wnt-Luc Reporter Gene assay (μM)</th>
<th>Capan-2 GI₅₀ (μM)</th>
<th>HPAF-II GI₅₀ (μM)</th>
</tr>
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<tbody>
<tr>
<td>0.06</td>
<td>2.66</td>
<td>5.18</td>
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**RXC004 is efficacious in a pancreatic cancer Capan-2 xenograft.**

Capan-2 cells were subcutaneously implanted into the flanks of SCID-Bg mice. Once tumours reached 200mm³ treatment with RXC004 was initiated orally for 28 days following both QD and BiD regimens.

A: RXC004 treatment results in significant TGR and TGI following both BiD and QD regimens.

B: PKPD post final dose (5mg/kg) show tumour drug levels in excess of the IC₅₀ for 24 hrs resulting in Wnt pathway inhibition. Axin2 mRNA levels measured by qPCR.

**SUMMARY**

- PK profile of RXC004 across pre-clinical species.
- IC₅₀ of the hERG ion channel is 12.7μM and in a dog CV safety study RXC004 displayed no adverse effects at all dose levels tested.
- RXC004 shows no inhibition of major CYP Isomers or activation of PXR in vitro.
- RXC004 is non-mutagenic in mini-Ames and micronucleus assays in vitro.
- RXC004 displays excellent selectivity in a CEREP safety panel, no counter-activities observed.
- RXC004 is deemed non-cytotoxic in a HepG2 cell cytotoxicity assay.

**RESEARCH**

- Redx porcupine inhibitor RXC004 exhibits potent and selective inhibition of the Wnt pathway in vitro and in vivo models of Wnt dependent pancreatic cancer.
- Preliminary results from both CT26 and B16 syngeneic mouse models indicate that RXC004 may enhance the efficacy of checkpoint inhibitors such as anti-PD1 antibodies by reducing the proportion of regulatory T cells in the tumour microenvironment and enhancing the ratio of CD8⁺ve to FOXP3⁺ve T-cells in tumour infiltrates.
- Pre-clinical studies are ongoing to determine the effect of RXC004 on immune response to cancer. RXC004 has been nominated as a candidate for development and IND enabling studies are in progress with First Time in Humans studies expected to begin early in 2017.

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**REFERENCES**