Porcupine inhibitor RXC004 enhances immune response in pre-clinical models of cancer

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Introduction

RXC004 is a potent and selective small molecule inhibitor of the membrane bound O-asparyl transerase Porcupine (PORCN). PORCN is required for post-translational modification of Wnt ligands, a necessary step in the initiation of canonical Wnt signalling (Figure 1).1) Aberrant Wnt signalling initiates key oncogenic pathways in cancer, implicated in tumour initiation, growth, cell senescence, cell death, differentiation and metastasis.2) Pre-clinical studies have demonstrated the potential for PORCN inhibition to provide benefit to molecularly selected cancer patient populations.3,4) RXC004 is currently being evaluated in a first-in-human clinical study (NCT03447470).

A growing body of literature suggests that Wnt signalling plays a role in the host immune response to tumours, and activation of the pathway may result in poor response and indeed resistance to immune checkpoint inhibitors.5) RXC004 has undergone preliminary evaluation in syngeneic mouse models of immunotherapy demonstrating its potential to enhance immune response in the tumour microenvironment. Early in vitro work using human primary cells is consistent with this hypothesis.

Results

RXC004 enhances the anti-tumour effects of anti-PD-1

Wnt pathway activation induces immunosuppressive human moDCs

RXC004 blocks secretion and function of Wnts

RXC004 blocks secretion of Wnts

RXC004 efficacy in B16F10 tumours requires an intact immune system

RXC004 reduces myeloid-derived suppressor cells from 'cold' tumours

Conclusions

• Consistent with the proposed role of the Wnt pathway in host immune response, RXC004 potently inhibits Wnt ligand secretion and thus enhances the immune response in the tumour microenvironment.
• Wnt pathway activation in immature human moDCs results in the formation of an immunosuppressive dendritic cell phenotype with increased IDD expression.
• Two immunomodulatory mechanisms have been observed and are being further investigated: 1) RXC004/anti-PD-1 combination in a CT26 syngeneic mouse colon tumour model (responsible to immune checkpoint inhibition) significantly increases the ratio of cytotoxic to regulatory T cells in tumour infiltrate via reduction of FOXP3+ Tregs. 2) Porcupine monotherapy in a B16F10 syngeneic mouse melanoma model (immunologically cold) results in tumour growth inhibition by reducing myeloid derived suppressor cell populations in the tumour microenvironment.
• RXC004 is currently under evaluation in a first-in-human clinical study and early human PK indicates drug exposure levels predicted for a clinical effect are achievable.

References