EFFECTIVE CO-TARGETING OF FIBROTIC AND IMMUNE MICROENVIRONMENTS TO IMPROVE THE OVERALL ANTI-TUMOUR RESPONSE IN MODELS OF ADVANCED PANCREATIC CANCER

Benjamin McLean, Diego Chacon Fajardo, Aji Istadi, Sean Porazinski, Marina Pajic, Marina Pajic*. Garvan Institute of Medical Research, Sydney, Australia

**Background**
Pancreatic ductal adenocarcinoma (PDA) has a 5-year survival of only 10% and persists as the 3rd most common cause of cancer-related death in Western societies. New treatment options are urgently needed. We have previously defined specific molecular subgroups of PDA associated with pre-clinical and clinical response to select tailored treatment strategies.1-2 One such molecular-guided therapy, RXC004, a potent and selective inhibitor of the Wnt/β-Catenin pathway regulator porcupine, is being investigated in a Ph2 study in patients with pancreatic cancer (NCT04907851). We have previously demonstrated interesting effects of tumour-cell targeted therapies on the environment of PDA.2-4

**Methods**
We determined the preclinical efficacy and detailed antistromal effects of RXC004 and selective ROCK2 inhibitors in a range of patient derived and genetically-defined PDA models, including clinically relevant combinations with standard of care (SoC) chemotherapy and immunotherapy. Mechanistic assessment of alterations in tumour cell-stromal cell cross-talk was performed using comprehensive transcriptomics and immunofluorescence approaches.

**Results**
In addition to reducing tumour growth and improving overall survival in patient-derived models of aggressive PDA, RXC004 demonstrated striking antifibrotic effects in vivo, with changes in cancer-associated fibroblast phenotype, accompanied by decreased levels of extracellular matrix components (fibronectin, peristin) and their organisation (collagen). Moreover, treatment with RXC004 as part of ‘priming’ combination therapy or ‘maintenance’ regimen significantly improved in vivo chemosensitivity. We also demonstrate that titrated modulation of fibrotic elements in vivo via ROCK2 targeting and as part of clinically-applicable therapeutic regimens, can lead to improved outcomes in diverse highly fibrotic and chemoresistant in vivo settings. Importantly, selective modulation of ROCK2 or Wnt signalling within the microenvironment of the immunocompetent LSL-KrasG12D/++; LSL-Trp53R172H/++; Pdx1-Cre (KPC) model of metastatic PDA revealed significant positive modulation of distinct immune components. These alterations include decreased level of immunosuppressive regulatory T cells, improved CD8+ and CD4+ T cell infiltration and increased presence of M1 pro-inflammatory macrophages in KPC tumours post-treatment, evident both within the tumour body and the invasive edge.

**Conclusions**
These data demonstrate that therapeutic efficacy of RXC004 and select anti-fibrotics in preclinical development may be the result of targeting both tumour cells and key aspects of the fibrotic and immune PDA microenvironment and in addition provide scientific rationale for the design of future SoC chemotherapy as well as immunotherapy-based combinations in pancreatic cancer.

**REFERENCES**

**Ethics Approval**
This study has been approved by the Garvan Institute of Medical Research/St Vincent’s Hospital Animal Ethics Committee.