Pancreatic cancer (PC) is the fourth leading cause of cancer death with an overall survival rate of less than 8%, and has a poor response rate to the current standard of care treatment of Gemcitabine and Abraxane. Recent large scale genomic studies have identified the Src/JAK/STAT3 pathway to be deregulated in up to 35% of PC patients, however it has yet to be systematically examined. In addition, due to the pathways important role in both tumour progression and immunosuppression, it is promising target for the development of novel personalised treatment strategies involving JAK and Src-inhibitors in PC.

**BACKGROUND**

**OBJECTIVES**

- Systematically examine the *in vitro and in vivo* efficacy of individualised therapeutic strategies involving a selective JAK1/2 (Ruxolitinib), and an Src inhibitor (Dasatinib).
- Investigate underlying mechanisms of efficacy in the context of the complex tumour microenvironment.

**METHODS**

We utilized well-characterised pre-clinical models, namely the patient-derived cell lines (PDCls, n=20), as well as cells from the genetically engineered mouse model of PC (Pdx1Cre; KrasLSL.G12D/+; p53R172H/+ or KPC)).

*In vitro* efficacy of JAK/Src-inhibitors was assessed using cell-proliferation assays and 2D drug synergy screens. Effect on 3D cell invasion was determined using organotypic assays.

Extra-cellular matrix (ECM) integrity post-treatment was assessed using 3D collagen-fibroblast contraction assays followed by second-harmonic generation (SHG) imaging and picrosirius staining.

*In vivo* efficacy was assessed using a subcutaneous, syngeneic KPC tumour model.

**RESULTS**

Src/JAK/STAT3 pathway is altered in PC

*Key JAK/STAT3 pathway components predict Ruxolitinib sensitivity*

**CONCLUSIONS**

Our preliminary *in vitro and in vivo* findings suggest that the combination of JAK and Src-inhibitors may be of therapeutic benefit in pre-defined subtypes of PC. The potential to target this pathway lies in the ability to improve the dense, immunosuppressive tumour microenvironment as well as target tumour cells.

Future work will involve examining the *in vivo* efficacy of these strategies in patient-derived xenografts, mechanistic studies, and validation of predictive biomarkers.

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