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Introduction Despite improved clinical results seen across a wide range of cancers due to the application of immunotherapies (IO), less than 1% of pancreatic cancers (PC) will respond to IO due to a multitude of factors, including poor tumour cell antigenicity and defective antigen presentation, low rates of mismatch repair deficiency, and an immunosuppressive tumour microenvironment (TME)[1]. Research to improve PC response to IO is limited to genetically engineered immunocompetent murine models of PC, which are driven by relatively few mutations that fail to recapitulate the true heterogeneity of this disease, while studies utilising patient-derived xenograft (PDX) models are limited to immunodeficient murine models[2]. To circumvent these issues, we have generated an immune-humanised mouse model for PC research.

Methods/Results We generated an HLA-typed biobank of umbilical cord blood-derived huCD34+ stem cells for intrahepatic engraftment into immunodeficient mice. We compared 4 strains of immunodeficient mice to optimise huCD45+ cell engraftment, monitoring haematopoietic cell engraftment and differentiation using multiparameter flow cytometry, and identified NSG-SGM3 and NBSGW mice strains as highest engrafted. We then engrafted HLA-matched immune cells and PC PDX in these strains of mice and monitored tumour and immune engraftment and tolerance. Finally, we analysed tumour and immune response to treatment utilising flow cytometry and spatial analysis techniques.

Conclusion We have identified the optimal immunodeficient mouse strain for huCD34+ stem cell humanisation, and successfully engrafted HLA-matched PC tumour cells and immune cells to investigate tumour response to combination anti-fibrotic drugs and IO.

References:

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2. Ju, Y., et al., *Barriers and opportunities in pancreatic cancer immunotherapy*. npj Precision Oncology, 2024. **8**(1): p. 199.

