Heterogeneity of Pancreatic Cancer – Implications for Future Therapies?

Treatment resistance of pancreatic cancer (PDAC) depends on cancer cell intrinsic mechanisms and an immunosupressive tumor stroma that supports tumour growth. Mouse models have provided important insights into the evolution of this highly lethal tumour, but there are no models that allow secondary genetic manipulation of autochthonous tumours, the immune system or the metastatic host niche once the tumour has formed. We generated novel PDAC models that permit spatial and temporal control of gene expression and modelling of PDAC subtypes and their respective microenvironments. These tools provide unparalleled access to the native biology of cancer cells and their hosting stroma, and rigorous genetic validation of candidate therapeutic targets in autochthonous tumours and subtype specific drivers in the immune system. Using these models we show that distinct routes of PDAC development exist that have an important impact on PDAC biology, phenotypic diversification, treatment response and resistance. Integration of cell culture genomes, transcriptomes and tumour phenotypes with functional studies and microenvironmental data revealed distinct effects of driver pathways on cancer evolution, heterogeneity and aggressiveness as well as the composition of the tumor microenvironment, the function of immune cells and therapeutic outcome.