The impact of the tumour microenvironment and the peri-tumour extracellular matrix on metastasis presents an opportunity to develop new therapies. Pancreatic tumours are especially fibrotic, causing starvation for nutrients and enhancing invasive behaviour. We are studying how tumour cells balance the usage of their cytoskeletal machinery to migrate and invade, with the assembly of macropinocytic structures to take up nutrients and thus survive in nutrient-depleted conditions. We aim to exploit vulnerabilities caused by the cancer microenvironment that could be targeted against metastasis and to model the metastatic niche using bioengineering.

One of the ways that tumour cells survive in the hostile tumour microenvironment is by repurposing their actin cytoskeletal migration machinery to take in large gulps of the surrounding liquid by macropinocytosis. Migration and macropinocytosis use the same basic actin machinery, and therefore can compete with each other - but the mechanisms controlling this competition are not well understood. PhD student Anh Le recently discovered an important role for the RAC1-interacting protein CYRI-A in regulating the balance between macropinocytosis and invasive cell migration (Le et al., 2021, Journal of Cell Biology). Together with PhD student Savvas Nikolaou, they found that CYRI-A and CYRI-B were both important in resolving macropinocytic cups, by opposing actin assembly and allowing action to disassemble for engulfment of macropinosomes. Interestingly, cells depleted of CYRI-A and CYRI-B were unable to perform macropinocytosis, but showed enhanced invasive migration, suggesting a competition between these processes (Le et al., 2021, Journal of Cell Biology; Le & Machesky, 2022, Bio. Protoc.).

Figure 1
Polyethylene glycol (PEG) hydrogels functionalised with fibronectin and collagen I provide a scaffold for 3D cell culture (top left: PEG hydrogel). This synthetic hydrogel mimics the biochemical and physical properties of the extracellular matrix to support growth of pancreatic ductal adenocarcinoma (PDAC) spheroids (top right: PDAC cell culture in PEG hydrogel; fibronectin (yellow), collagen 1 (cyan), phalacidin (purple), DAPI (blue)). Co-culture of PDAC cells and liver spheroids within the PEG hydrogel provides a 3D in vitro model of PDAC metastasis in the liver (bottom left: co-culture of PDAC cells and liver spheroids; collagen 1 (magenta), DAPI (cyan), phalacidin (red) and bottom right co-culture with PEG hydrogels: PDAC cells (green), liver spheroid (grey)).

Collagen-6 was upregulated and its expression contributed to invasive migration and establishment of metastases. Collagen-6 could be produced both by cancer cells and stromal cells and our study suggested that it could be expressed early during metastasis as an important promoter of a new metastatic niche in pancreatic ductal adenocarcinoma.

PhD student Hakem Albilasi is studying the interactions between chronic myeloid leukaemia (CML) cells and mesenchymal stem cells. He found that CML cells can interact with mesenchymal stem cells and is studying the mechanisms and consequences of this interaction.

PhD students Sonia Rolo and Elaine Ma are studying the effects of mechanosensing on expression of various target genes involved in invasion and migration in pancreatic ductal adenocarcinoma. Elaine is also developing novel hydrogels for the culture of tumour cells and organoids in conditions where she can use bioengineering to control stiffness and composition of the matrix (Figure 1). These hydrogels will serve as an excellent platform to ask specific questions about the effects of physical parameters and matrix composition on the 3D growth of cancer cells. Juda Milvidaite is also exploring bioengineered materials, such as alginate hydrogels, for the growth and preservation of organoids and tumour samples in collaboration with the Biotech company Aletheis. Together, we are developing new models for the tumour and metastatic niche to build better models of the complex cancer microenvironment.

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