DESCRIPTION FOR THE GENERAL PUBLIC

Currently available therapeutic options for patients with advanced metastatic disease are highly limited. Unfortunately, 90% of cancer patients die due to resistance to treatment and metastases formation. Detailed insights into the mechanisms that control metastasis are the only chance to reveal novel opportunities for intervention at different stages of metastatic progression.

The mechanism of metastasis remains poorly understood. However, by identifying a range of genes and molecules involved, we start to understand particular processes and reveal a complex picture of metastatic evolution. During the metastatic process, cells disseminate, invade and migrate to distant secondary sites. The ability to metastasise results from the epithelial to mesenchymal transition (EMT) program activated in cancer cells. The EMT happens when polarised epithelial cells (the origin of 90% of all cancers) differentiate into mobile mesenchymal cells. It has become broadly understood that EMT is not a binary switch between epithelial or mesenchymal states. Tumour mass represent different intermediate forms between the full epithelial and full mesenchymal phenotype (hybrid E/M, EM plasticity), with various expression of epithelial and mesenchymal markers. Hybrid E/M states exhibit differences in invasion capacity and metastatic potential. The mechanism of their regulation is not known.

The main objective of this project is to investigate the role of MLK4 mutations in EM plasticity control and contribution to metastasis formation. Mixed-lineage kinase 4 (MLK4) is a serine/threonine protein kinase regulating several signalling pathways implicated in cancer pathogenesis. We have recently proven correlation between high MLK4 and expression of mesenchymal markers. Our project will integrate the most powerful techniques in molecular biology: RNA-seq and mass spectrometry, for transcriptome and proteome analysis, respectively; as well as functional *in vitro* and *in vivo* studies.