Project Title: **"Role of the metastatic niche in organ-specific SCLC metastasis"**
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Research Group: **Small Cell Lung Cancer Biology Group, CRUK Manchester Institute**

Metastases are the predominant cause of cancer-related deaths, yet they remain difficult to study due to their spatial and temporally sporadic occurrence. This unmet clinical need is starkly exemplified in Small Cell Lung Cancer (SCLC), one of the most metastatic of all cancers. SCLC is an incurable neuroendocrine (NE) carcinoma and most patients live less than one year after diagnosis. More than 80% of patients are diagnosed with oligo-metastatic disease, including to the liver, lymph nodes, adrenals, bone and brain. Effective therapies to limit and target metastases are urgently needed. It is difficult to obtain metastatic biopsies from patients with SCLC and Genetically Engineered Mouse Models (GEMMs) of SCLC do not metastasise with reliable frequency, or with the same organ-tropism as observed in patients. This challenge is partially overcome in our biobank of >65 CTC-derived patient explant models (CDX) in immunodeficient mice, which are faithful models of the donor's disease. Multiple CDX models metastasise reproducibly and spontaneously following resection of the subcutaneous tumour. Moreover, their metastatic distribution largely recapitulates that of patients with SCLC, including to the brain and liver[1,2]. This approach enables molecular and functional studies to address properties of metastasic seeding and colonisation at these organ sites.

In collaboration with the Ilaria Malanchi (Tumour-Host Interaction Lab, Francis-Crick Institute), this project aims to address a fundamental aspect of metastasis biology in SCLC. Their unique mCherry-niche labelling system enables identification of host-tumour cell interactions in the metastatic niche in vivo[3]. By incorporating this labelling technology into our metastatic CDX studies, we aim to define host-tumour cell interactions that support tumour growth within different organs. In parallel, syngeneic SCLC GEMM xenografts established in immune-competent hosts will be evaluated under our resection protocol to incorporate the role of the immune tumour microenvironment in metastatic niche formation using the same approach. Phenotypic and molecular profiling of interacting tumour and host cells within the niche via multiplex immunofluorescence and multi-omic spatial profiling will inform on tumour intrinsic and extrinsic features enabling metastases and contributing to organ tropism. Specific candidates that support niche formation and metastasis in SCLC will be functionally validated in ex vivo co-culture assays (e.g., genetic manipulation followed by metabolic and phenotypic profiling). In vivo studies will assess their contribution to organ-specific metastasis and patient samples will be evaluated with the aim to define novel biomarkers or therapeutic targets to detect and/or limit metastasis in patients with SCLC.

Beyond the strengths of the CRUK Manchester Institute, this project will benefit from our group's close alignment with the CRUK National Biomarker Centre (NBC) (https://cruknbc.org/) and the wide range of expertise therein. We make substantial use of multimodal molecular profiling techniques, which in turn utilise a wide variety of bioinformatics approaches. We utilise the latest *in vitro* and *in vivo* techniques and technologies for discovery of therapy target discovery and predictive biomarkers towards implementation of precision medicine.

References: [1]Simpson *et al.*, (2020) Nat Cancer 1: 437-451.[2]Catozzi et al., (2025) Cell Rep 44: 115803, [3]Ombrato et al., (2019) Nature 572:603-608