Small Cell Lung Cancer (SCLC) is characterised by rapid growth, prevalent circulating tumour cells (CTCs), and early metastasis. This aggressive neuroendocrine (NE) cancer has a poor prognosis with <1-year median survival. Effective, personalised therapies are urgently sought. Underpinning rapid disease evolution, SCLC is one of the most metastatic cancers where >80% patients present with metastatic disease frequently in the liver and the brain. Until recently, lack of robust patient-derived preclinical models and a paucity of SCLC biopsies hampered molecular studies of SCLC, and in particular, SCLC metastasis. Our lab developed >60 CTC-derived patient explant models (CDX) in immunodeficient mice which are faithful models of the donor’s disease. Using our newly developed SCLC *in vivo* resection protocol, multiple subcutaneously implanted then resected CDX models routinely and spontaneously metastasise to multiple organs with similar tropism to that observed in SCLC patients, including brain and liver. This project will utilise CDX models to study mechanisms of metastasis.

SCLC NE cells can transition to non-NE cells via NOTCH signalling; these rarer non-NE cells are relatively chemoresistant and, in mouse models of SCLC, non-NE cells are required for metastasis. We recently discovered using CDX models, that non-NE cells within SCLC tumours undergo further phenotypic transition via Vasculogenic Mimicry (VM) adopting endothelial cell behaviours with *de novo* formation of vessel-like structures that are associated with poorer patient outcomes (Williamson *et al.*. (2016) *Nature Communications*; Pearsall *et al.*. (2023) *Journal Thoracic Oncology*). VM is frequently observed in CDX models and we hypothesise that VM enables tumour growth under conditions of limiting oxygen/nutrients and supports tumour cell dissemination. Using metastatic CDX models, this project seeks to characterise the phenotypic plasticity that generates non-NE cells, subsequent formation of VM vessels and their functional significance in SCLC growth, therapy resistance and metastasis.

Our laboratory makes use of the latest *in vitro* and *in vivo* techniques and technologies to interrogate questions primarily concentrating on lung cancer, with the goal of developing novel treatments and predictive biomarkers to facilitate the implementation of precision medicine programs. We make substantial use of multimodal molecular profiling techniques, which in turn utilise a wide variety of bioinformatics approaches. We would be particularly happy to receive applications from individuals with a strong academic track record (First/upper-second class) and Masters-level and/or other laboratory research experience in cancer. The project will benefit from our Group’s close alignment with the adjacent CRUK Cancer Biomarker Centre ([https://www.cruk.manchester.ac.uk/Our-Research/Cancer-Biomarker-Centre](https://www.cruk.manchester.ac.uk/Our-Research/Cancer-Biomarker-Centre)).

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