Metastases are the predominant cause of cancer-related deaths. Small Cell Lung Cancer (SCLC), is an aggressive neuroendocrine (NE) tumour, representing ~13% of all lung cancers and is the 6th highest cause of cancer-related deaths worldwide. SCLC is one of the most metastatic cancers (>80% patients present with metastatic disease) with common sites including liver and brain, which are clinically challenging and remain incurable. Until now, lack of robust patient-derived preclinical models and a paucity of SCLC biopsies hampered molecular studies of 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 involve transcriptomic profiling of liver and brain-metastatic tumours from these mice, comparing single cell data from the mouse SCLC CTCs in order to define the molecular components responsible for liver- and brain-specific organ tropism and also employ spatial profiling (combined transcriptomic and protein-expression analysis) to understand the molecular features enabling metastatic colonisation of these organs. Functional validation of candidates will follow via their in vitro and in vivo manipulation using knockdown/over expression and CRISPR tools and pharmacological manipulation, with the ultimate aim to define their role in clinical specimens and identify novel therapeutic vulnerabilities to benefit SCLC patients in the future.

This 4-year PhD studentship will be based initially at the Cancer Research UK Manchester Institute, Alderley Park, Cheshire. The rebuilding of our world class research facilities is well underway, and we anticipate returning to our original site in Withington, Manchester, UK in 2023 next to the Christie NHS Foundation Trust

University of Manchester entry: September 2022