Project Title: “Dissecting the molecular mechanisms of chemoresistance in small cell lung cancer for identification of biomarkers and new drug targets”

Group Leader: Caroline Dive
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Research Group: Small Cell Lung Cancer Biology Group

Small Cell Lung Cancer (SCLC) is characterised by rapid growth, prevalent circulating tumour cells (CTCs), and early metastasis. In the majority of cases, this disease is initially highly sensitive to chemotherapy but within a matter of months patients relapse with acquired chemoresistance. Some patients (~30%) also present with extremely aggressive disease that does not respond to chemotherapy even in first line, termed chemorefractory. Beyond the almost universal inactivation of tumour suppressors TP53 and RB1 in SCLC, the genomic landscape is highly mutated and heterogeneous between patients, and more recent work in preclinical models had revealed extensive phenotypic heterogeneity, revealing plasticity and evolution under the selective pressure of chemotherapy. Acquiring tumour tissue is challenging in SCLC so in 2014, we pioneered patient CTC-derived explant mouse models (CDX) of SCLC, generated from a 10ml blood sample. We now have >60 CDX models, including ten pre- and post-chemotherapy CDX pairs from the same patient that will form the experimental basis of this proposal, enhanced by the large number of models that reflect either chemosensitive or chemoresistant disease (both in the patient, and in preclinical studies). We have Whole Genome Sequencing, RNA Sequencing and methylation profiling data on these models, and in addition to previously identified putative targets, the student will work with our Bioinformatics and Biostatistics Team to identify novel targets and pathways that can then be functionally interrogated to understand their role(s) in chemoresistance using a range of ex vivo cell fate experiments and in vivo studies. In addition to identification of drug resistance mechanisms we aim to discover new targets for mechanism-based therapies that can be tested second line after failure of standard treatment. The project seeks to characterise SCLC evolution through therapy, to explore mechanisms of chemo-resistance and discover novel therapy targets for translation into future benefit for people with SCLC. Beyond the strengths of the CRUK Manchester Institute, this project will benefit from our group’s close alignment with the CRUK Cancer Biomarker Centre (https://www.cruk.manchester.ac.uk/Our-Research/Cancer-Biomarker-Centre) and the wide range of expertise therein.

We are looking for a motivated, focussed, ambitious individual to join our Small Cell Lung Cancer Biology Group. We make 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. We will also consider applications from individuals with exceptional bioinformatics skills who are looking to expand their experience and training with wet lab work.

*This position has been generously funded by hundreds of donations to The University of Manchester's drug resistance in cancer appeal. The successful candidate will work with the University's fundraising team to keep donors up-to-date on their progress. This could include providing written updates and photographs, appearing in video content, attending events, or meeting donors. By doing this, you’ll help show donors the difference they are making, and inspire them to continue their support for our cancer research.*

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