Project title: Investigating drug resistance and sensitivity of emerging therapies in KRAS G12C mutated colon cancers.

Project Summary: The use of targeted therapies in KRASG12C mutated cancers is fast evolving. However, multiple challenges still remain. Firstly, multiple patients have innate resistance (do not have partial or complete response to the treatment with these inhibitors) and in those patients who do respond, have a limited progression free survival. Secondly KRAS G12C inhibitors have context specific outcomes (patients with lung cancers with KRASG12C mutations have better response rates than patients with colon or pancreatic cancer with the same mutation). The next generation of KRAS G12C inhibitors that target KRAS in the GTP bound 'on' state and pan RAS inhibitors may improve outcomes.

This project aims to answer two important questions related to innate resistance to KRAS G12C inhibitors in colon cancer.

Firstly, It aims to study the role of cancer associated fibroblasts in drug resistance in the setting of colorectal cancer. These can contribute to both innate and acquired resistance to KRAS inhibitors. We have developed a dual flow bioreactor which can pump culture medium between tissue culture flasks. We aim to use this technology to run whole genome CRISPR screens in KRASG12C mutated colon cancer cancer cells under selection pressure of KRAS G12C 'off,' KRAS G12C 'on' and pan KRAS inhibitors under conditions a) culture medium which is exposed to KRASG12C mutated cancer cells or b) culture medium exposed to colon cancer associated fibroblasts (CAFs). This will shed light on differences in genes associated with innate resistance to different classes of KRAS G12C inhibitors and importantly in addition, differences in genes important to sensitivity and resistance to KRAS G12C inhibitors that are grown in culture medium which have or have not been exposed to cancer associated fibroblasts. There is little data on the role of CAFs in the sensitivity or resistance to KRAS G12C inhibitors in colon cancer and this studentship will attempt to answer this. Currently clinical efforts are focused on combining first generation KRAS G12C inhibitors with the anti-EGFR antibody cetuximab which was based on targeted phosphoproteomic experiments studied in cancer cells alone with no stromal components.

The second aim of this project is to be able to predict the effects of anticancer drugs ex-vivo model systems. We have developed a 1cm x 1cm chip with a microfluidic solution to load drugs into 50-70 wells. This will allow us to expose these chips loaded with multiple individual drugs at different concentrations to xenograft tissue ex-vivo to study markers of proliferation such as Ki67 or cell death c-PARP or c-caspase 3 or gamma H2AX using multiplex immunohistochemistry platforms. It can also study down biomarkers of target inhibition such as p-ERK and p-AKT. Duration of exposure to the xenograft tissue will be optimized. The effects of drugs causing

early cell death in ex-vivo models can be tested on growth inhibition in xenograft models and be piloted in fresh surgical specimens/tumour biopsy tissue.

This ambitious PhD studentship will be open to oncologists in training who which to learn important molecular biology techniques and use engineering solutions developed inhouse to answer relevant clinical questions in an area of unmet need.

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Clinical Specialities: Medical Oncology, Clinical Oncology