Project title: Image based grading of liquid biopsies.

Project Summary: Metastasis is the most lethal feature of cancer. Recent reports suggest the prevalence of mitotic circulating tumour cells (CTCs) in aggressive late-stage breast cancer is a more accurate method of stratifying highly aggressive breast carcinomas and correlates with shortened overall survival. The development of CTC isolation methods has stalled over the last two decades and, its limitations notwithstanding, ctDNA profiling has become a more oft used method to track the progress of disease and its response to treatment. While multi-omic profiling of a patient's tumour and metastatic cells promises a future of personalised treatment, the spread of disease (i.e. stage) and its aggressiveness (i.e. grade) currently remain the two most clinically important factors in a patient's survival and treatment.

Our hypothesis is that gaining insight into CTC cell cycle / mitotic indexing might better stratify patients into prognostic groups and identify more aggressive cancer targets using a blood-based biopsy.

Based on this we aim to address the following questions:
i) Can we develop facile imaging methods to determine the cell cycle stage of patient derived primary CTCs?
ii) Can we use this as a readout of CTC therapy response in real time in patients with metastatic triple negative breast cancer (TNBC)?

A primary reason for limited clinical use of CTCs is the inability to translate prognostic applications into mainstream clinical treatment, invariably down to complexity of lab assays leading to significant costs. We also believe this is due to the current inability to accurately distinguish highly aggressive from less aggressive CTCs. This project will develop relatively cost-effective microscopy methods along with in-vitro/vivo modelling to identify more aggressive CTCs. CTC therapy response will be evaluated on the microfluidic chip in real-time using a panel of agents clinically approved for metastatic TNBC. This project will pave the way for accurate prognostic and therapeutic stratification of highly aggressive TNBC patients.

The team brings together a mix of well-established medical and molecular research oncologists as well as multidisciplinary scientists from Imperial College and the ICR. The Salehi-Reyhani lab develops microfluidic systems capable of isolating CTCs and determining on-chip drug efficacy with single cell resolution for translation into the clinic. The Natrajan lab focusses on understanding and targeting drivers of epigenetic and transcriptional plasticity in treatment resistant breast cancers using in vitro and in vivo models to develop new biomarkers and therapeutic targets. The project brings to bear molecular biology, microscopy, and machine learning on an unmet need in breast cancer research and treatment. This is clearly a task that is not

possible without a team-based convergence science approach suited to clinicians with an interest in academic research.

Supervisory Team: Dr Ali Salehi-Reyhani, Dr Rachael Natrajan

Clinical Specialities: N/A