CANCER RESEARCH UK CLINICAL ACADEMIC TRAINING PROGRAMME
ICR The Institute of Cancer Research
IMPERIAL

Project title: Modelling spatial features, interactions and transcriptional profiles at single-cell resolution that associate with CDK4/6 inhibitor treatment resistance in breast cancer

Project Summary: In post-menopausal women, aromatase inhibitors (AromIs) are used to block production of estrogens in estrogen receptor positive tumors to reduce breast cancer relapse and mortality. For patients with a higher risk of recurrence, it is now standard to also receive CDK4/6 inhibitors (CDK4/6Is) for better outcomes. There is a strong association between early relapse and the presence of cancer cells that remain proliferative after treatment, but there is a large gap in the understanding of the drivers of resistance. Some major features of resistance in treatment have been identified in bulk transcriptome and whole exome sequencing analysis (e.g. low expression of the ER in AromIs treatment, *CCNE1* over expression in AromI + CDK4/6I treatment); however, the driver of resistance is unknown in the majority of patients. We have a unique set of samples from the PALLET clinical trial (NCT02296801) that randomised 309 patients to 2 weeks of AromI or AromI+CDK4/6I, and at 14 weeks of AromI-only or AromI+CDK4/6I treatment. The fellow will generate single-cell whole transcriptomic on a subset of these samples at baseline and after 2 and 14 weeks of treatment. The aims of the training fellowship would be to identify those cells that are still proliferating after AromI and CDK4/6I treatment and to identify the molecular features of these cancer cells, together with cell-cell interactions and tumour microenvironments associated with those proliferating cells. Bulk RNA and DNA sequencing data is already available for these samples, and together with the spatial single cell data, the aim will be to identify biomarkers associated with treatment resistance. A background in mathematics, at A level, as well as an interest to learn computational biology, is required for this training fellowship. Full training in computational biology will be supplied.

There are several single-cell transcriptomics and proteomics analysis projects currently on-going in the Ralph Lauren Breast Cancer Research Centre, including a spatial tissue microarray study of ~1000 tumours. The fellow will be able to take advantage of the analysis pipelines and expertise in the lab to have greater focus on the PALLET spatial transcriptomics project. The fellow will also be able to take advantage of bulk sequencing data that has already been analysed on the PALLET samples and use this data to work toward development of biomarker assays for CDK4/6Is resistance in breast cancer.

Supervisory Team:

Prof. Nick Turner (ICR): Prof Turner is the Head of the Ralph Lauren Breast Cancer Research Centre at the Royal Marsden Hospital and Group Leader of the Molecular Oncology Team at the Institute of Cance Research (ICR). Prof Turner has led the clinical development of multiple breast cancer treatments including the CDK4/6 inhibitor palbociclib and the AKT inhibitor capivasertib. His preclinical work identified the synergy of combining CDK4/6 and PI3 kinase inhibition leading to the practice chanding INAVO120 phase III trial and the registration of the PI3 kinase inhibitor inavolisib. On-going projects include clinical potential of cell-free DNA in breast cancer and the Breast Cancer Research Foundation grant on spatial transcriptomics and proteomics analysis of tumours from transATAC.

Prof. Vahid Shahrezaei (Imperial): Prof. Shahrezaei is a Biomathematician based at the Department of Mathematics, Imperial College London. Since 2008 his research has focused on causes and consequences of phenotypic cell-to-cell variability such as noise in gene expression in health and disease. He has done seminal work on using mathematical modelling to understand the role of intrinsic noise and cell cycle in stochastic gene expression. More recently he has used statistical and machine learning approaches to understand mechanisms of stochastic and cell-cycle regulated gene-expression from single-cell RNA sequencing. Through these approaches he has contributed to the understanding of the role of epigenetic regulation in cancer evolution and the role of injury in the development of Glioblastoma.

Dr. Eugene Schuster (ICR): Dr. Schuster's work in the last 10 years at the ICR has focused on multi-omics projects of resistance to treatment mechanisms in ER+HER2- clinical and pre-clinical studies including work on mechanisms of resistance to aromatase inhibitors and CDK4/6 inhibitors, with additional work on ER+HER2+ BC and sarcoma. Dr. Schuster's research on pre-clinical and clinical datasets has resulted in a gene expression based predictive test for combined aromatase inhibitor and CDK4/6 inhibitor treatment (patent GB2116745.7; *Prognostic and Treatment Response Predictive Method*) used in the Phase III POETIC-A trial of hormone therapy and abemaciclib treatment (NCT04584853). Dr Schuster leads the bioinformatics analysis of the spatial transcriptomics and proteomics analysis of tumours from the transATAC study.

Clinical Specialities: Medical Oncology, Clinical Oncology, Pathology