PhD Project Proposal

Funder details

Studentship funded by:	MRC iCASE (AstraZeneca)

Project details

Project title:	Computational and Multi-omic Profiling of Resistant Tumour Cell Subclones in Oestrogen Receptor-Positive Breast Cancer

Supervisory team

Primary Supervisor:	Maggie Cheang
Associate Supervisor(s):	Christopher Morrow (AstraZeneca) Eugene Schuster
Secondary Supervisor:	Nicholas Turner

Divisional affiliation

Primary Division:	Clinical Studies
Primary Team:	Integrative Genomics Analysis in Clinical Trials
Site:	Sutton

Project background

Over 80% of breast cancer (BC) patients in the developed western world have oestrogen receptor (ER)–positive disease. Standard treatment typically includes surgery and adjuvant endocrine therapy (ET), with chemotherapy used in some cases, and these approaches have substantially improved survival outcomes (1). In postmenopausal women, aromatase inhibitors (AIs) are among the most effective endocrine therapy agents. Despite this, many patients still recur because of de novo or acquired, resistance to AI treatment.

CDK4/6 inhibitors are now approved in US and UK for high-risk, node positive hormone receptor (HR)+/HER2- early BC, supported by results from the phase III MonarchE randomised controlled trial (2). However, HR+/HER2+ BCs are molecularly heterogeneous, with around 30% of these tumours classified as HER2-Enriched (HER2-E). We have shown that HR+/HER2-E BC is characterised by an immune-activated stroma, elevated tumour infiltrating lymphocytes, lower expression of luminal-related genes than the HR+/Luminal subtypes, and have greater benefit from anti-HER2 therapies than from endocrine therapy(3).

Resistance to ET has been studied mainly in HR+/HER2- BC, but those mechanisms may differ between HER2+ and HER2- tumours. In addition, tumour cells within the same cancer can be genetically diverse and respond differently to treatment, allowing small resistant populations to persist and potentially drive recurrence.

The PeriOperative Endocrine-Therapy for Individualised Care (POETIC) trial (4) provides a unique framework to study endocrine resistance mechanisms in a large set of ER+ HER2+ and HER2- BC patients. This PhD project will use computational and molecular approaches to isolate resistant tumour cells and identify genomic alterations specific to them, generating insight into treatment resistance and supporting more precise, personalised therapy.

Project aims

- To define the molecular features that distinguish ER+/Ki67+persistent (proliferating) tumour cells from the non-proliferating cells following peri-operative aromatase inhibitor treatment (AIs).
- To assess whether genomic markers identified in the Ki67-persistent tumour cells after 2 weeks of peri-operative AIs are retained in local and distant recurrent disease.
- To identify candidate drug targets and therapeutic opportunities through comparative analysis of resistant-cell multi-omics and profiles from ER+ cell lines models exposed to investigational compounds at AstraZeneca

Research proposal

Mechanisms of resistance to aromatase inhibitors (AIs) vary between patients, and the rational use of the growing number of targeted agents for endocrine resistance will require new ways of identifying the specific resistance mechanisms operating within individual tumours. This project will address that challenge by analysing data and samples from the POETIC (Peri-Operative Endocrine Therapy – Individualising Care) study (4). POETIC was an open-label, multicentre, parallel-group, randomised, phase 3 trial (done in 130 UK hospitals) in which 4480 postmenopausal women aged 50 years or older with WHO performance status 0–1 and ER+, operable breast cancer were randomly assigned (2:1) to receive peri-operative AI treatment (POAI) (letrozole 2·5 mg per day orally or anastrozole 1 mg per day orally) for 14 days before and after surgery or no POAI (control). Adjuvant treatment was given as per UK standard local practice. In this cohort, we showed that KI67 levels, and changes Ki67 after POAI, were associated with time to recurrence (TTR) and overall survival (OS) (4). The Ki67 value was measured using a standardised visual scoring method in which stained and unstained invasive tumour nuclei were counted across at least 5 high-power fields (i.e., the most representing field); the Ki67 staining index was calculated as the proportion of stained invasive nuclei.

Intratumor heterogeneity of Ki67 expression after neoadjuvant endocrine therapy is thought to be associated with poor outcomes and treatment resistance but datasets and analytical approaches capable of resolving molecular differences between the resistant and sensitive subclones remain limited. The central biological question is whether persistent Ki67-positive cell populations represent resistant clonal populations that continue to survive under treatment pressure and ultimately drive micro-metastatic outgrowth and recurrent disease . This broader question can be broken down into three components.

First, are the ER+/Ki67+ persistent proliferating cells at 2 weeks molecularly distinct, either genetically or epigenetically, from the non-proliferating cells? In pilot project, multi-parameter fluorescence-activated cell (FACS) applied to 26 AI-treated FFPE POETIC samples collected at 2 weeks enabled separation of de novo AI-resistant from sensitive cell populations and, whole-genome sequencing showed a higher mutational burden in the AI-resistant populations at presentation (5). These early data suggest that systematic comparison of proliferative and non-proliferative tumour cell populations may identify putative drivers of resistance in individual tumours. This FACS-based approach provides an effective bridge between approaches that are lower-cost but labour-intensive methods that provide only limited resolution of tumour heterogeneity, such as needle microdissection, and high-cost approaches that provide a much richer view of heterogeneity, such as spatially resolved single cell sequencing.

As single-cell and spatial omics methods for FFPE tissues continue to evolve, the project will evaluate data from platforms such as cyclic immunofluorescence, 10x Visium, GeoMx Digital Spatial Profiling, and/or CosMx Spatial Molecular Imager. A major computational component of this project will be the development of approaches to integrate these data with digital pathology, including high-throughput image analysis and machine learning/artificial intelligence, in order to quantify morphological and biomarker-defined tumour subpopulations. Combining digital pathology with spatial and bulk multi-omics will allow us to interrogate resistant clones within their native microenvironment, and to connect patterns with molecular features at scale.

We will also examine whether resistant clones stratify according to HER2 status or intrinsic subtypes**.** A further key question is whether multi-omic markers identified in Ki67-persistent cells at 2 weeks are also detectable in recurrent disease, and whether these differ between locoregional and distant recurrence. POETIC provides a unique opportunity to address this. The protocol includes optional recurrence sample collection at the time of relapse. This will enable systematic comparison of multi-omic markers across matched primary tumours, locoregional recurrence, and distant recurrence, and will provide a clinically relevant framework for studying how early resistant-cell states relate to later disease progression.

Finally, this PhD project will investigate whether improved treatment strategies can be identified for AI–resistant clones. In collaboration with Translational Medicine and Bioscience colleagues at AstraZeneca, genomic and phenotypic features of resistant tumour cell populations will be compared with data from ER+ cell lines and patient-derived cancer models treated with investigational compounds. This comparative analysis will help to assess resistant-cell states align with responses to next-generation endocrine therapies or novel therapeutic combinations. The aim is to identify alternative therapeutic strategies, refine biomarkers for patient stratification, and define biological endpoints that could support adaptive, clinical trial designs.

By incorporating digital pathology, spatial omics, and bulk multi-omics, and clinically annotated trial data, this PhD project will generate a multi-layered view of endocrine resistance biology. It will be particularly suitable for students interested in **computational biology, data science, machine learning, quantitative pathology, and translational genomics**, while retaining strong links to clinical and experimental cancer research. Through partnership with AstraZeneca, the student will gain experience in both forward and reverse translation, and in how computational and molecular analysis can inform the design of next-generation precision oncology trials.

Literature references

[1] Sirvén MB, López-Knowles E, Zhu X, et al. Short-duration preoperative endocrine therapy alters molecular profiles to predict favourable outcome in ER+/HER2+ early breast cancer: a POETIC translational study. EBioMedicine. 2025 Aug;118:105823. doi: 10.1016/j.ebiom.2025.105823. Epub 2025 Jul 18.

[2] Schuster EF, Lopez-Knowles E, Alataki A et al. Molecular profiling of aromatase inhibitor sensitive and resistant ER+HER2- postmenopausal breast cancers. Nat Commun. 2023 Jul 7;14(1):4017. doi: 10.1038/s41467-023-39613-z.

[3] Early Breast Cancer Trialists' Collaborative G.: Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022;23(3):382-92

[4] Martin M, Hegg R, Kim SB, et al.: Treatment with adjuvant abemaciclib plus endocrine therapy in patients with high-risk early breast cancer who received neoadjuvant chemotherapy: a prespecified analysis of the monarchE randomized clinical trial. JAMA Oncol. 2022 Aug 1;8(8):1190-1194.

[5] Bergamino MA, López-Knowles E, Morani G, et al.: HER2-enriched subtype and novel molecular subgroups drive aromatase inhibitor resistance and an increased risk of relapse in early ER+/HER2+ breast cancer. eBioMedicine,2022.

[6] I Smith, J Robertson, L Kilburn, et al.: Long-term outcome and prognostic value of Ki67 after perioperative endocrine therapy in postmenopausal women with hormone-sensitive early breast cancer (POETIC): an open-label, multicentre, parallel-group, randomised, phase 3 trial Lancet Oncol, 21 (2020), pp. 1443-1454

[7] Schuster ER, Zabalgo L, Perou CP, et al.: Multi-parameter FACS sorting identifies higher mutational burden in aromatase inhibitor resistant subclones in estrogen positive breast cancer at diagnosis San Antonio Breast Cancer Symposium; 2019 Dec 10-14; San Antonio, TX. Philadelphia (PA)2019.

Candidate profile

Note: the ICR’s standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:	• Candidates must have a First or 2:1 Honours degree or a master’s in computer science, mathematics, engineering, statistics, or a related discipline. • Knowledge of cancer biology, cell biology, digital pathology or analytical chemistry • Strong presentation and communication skills • Previous laboratory experience (desirable but not essential)
Intended learning outcomes:	• Knowledge in data from next-generation sequencing, molecular pathology, molecular diagnostics.

	- Knowledge in experimental skills in molecular techniques including spatial omics and single-cell sequencing. - Advanced medical statistical skills. - Ability to apply machine learning and artificial intelligence to biomedical data - Ability to design, manage and progress a defined scientific project. - Scientific writing, presenting and communication skills. - Ability to read and process relevant literature.

Advertising details

Project suitable for a student with a background in:	☒ Biological Sciences ☒ Physics or Engineering ☐ Chemistry ☒ Maths, Statistics or Epidemiology ☒ Computer Science