ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	**Evolutionary Medical Genomics Doctoral Network (EU funding)**

Project details

Project title:	**New strategies for exploiting the fitness costs of drug resistance in cancer**

Supervisory team

Primary Supervisor:	**Prof Trevor Graham**
Associate Supervisor(s):	**Dr Annie Baker, Dr Freddie Whiting, Dr Erica Oliveira**
Secondary Supervisor:	**Dr Rachael Natrajan**

Divisional affiliation

Primary Division:	**Cancer Biology**
Primary Team:	**Genomics and Evolutionary Dynamics**
Site:	**Sutton**

Project background

Drug resistance is a major clinical challenge in cancer treatment, underlying both tumour recurrence and patient mortality (Vasan et al, 2019). Yet when cancer cells develop resistance to a drug, there can be an evolutionary "trade-off" that occurs as cells allocate resources to resistance rather than to other cellular functions such as proliferation (Aktipis et al, 2013). This means that resistant cells may have reduced fitness in a drug-free environment. The idea of a "fitness cost to resistance" underpins a series of new strategies for the "adaptive treatment" of tumours, in which a population of drug-sensitive cells are maintained, and when the drug is removed these can then out-compete the drug-resistant population (Gatenby et al, 2009). Re-introducing the drug can then be effective at reducing tumour burden as there is a significant population of sensitive cells that will die. Such adaptive interventions could provide a route to circumvent drug resistance, by controlling a tumour rather than attempting to eradicate it.

For adaptive therapies to reach their potential in the clinic, we need a deeper understanding of the factors that influence the cost of resistance; tumour (epi)genetics, therapy type, microenvironment, and mechanism of resistance are all likely to be important. This project proposes to systematically characterise the mechanisms and fitness costs of resistance by performing a large-scale experimental screen across diverse cancer cell lines exposed to a range of standard-of-care drugs.

We previously showed that resistance to platinum chemotherapy has a fitness cost for ovarian cancer cells (Hockings et al, 2025), and subsequently opened a clinical trial testing adaptive dosing of chemotherapy in patients with this disease (Mukherjee et al, 2024). We also developed a mathematical modelling framework that infers the temporal dynamics of cancer cell drug resistance phenotypes using only genetic lineage tracing and population size data (Whiting et al, 2025). This project will build upon this methodology, with the aim of identifying novel therapeutic strategies where adaptive dosing could be used to outcompete resistant clones.

This project is part of the EU-funded Evolutionary Medical Genomics Doctoral Network (EvoMG-DN), which is currently recruiting a cohort of 15 PhD students based at leading universities, research institutes, and industry partners across 7 European countries. The programme offers the students multiple travel opportunities, summer schools, and placements in other participating labs across Europe.

Project aims

- Barcode a panel of cancer cell lines to enable genetic lineage tracing
- Design a large-scale experimental screen in which clinically relevant drugs are applied to barcoded cancer cell lines, generating resistant clones in vitro
- Use single cell DNA sequencing to track genetic lineages through treatment and resistance, and single cell RNA sequencing to characterise the resistant phenotype
- Apply mathematical frameworks to learn the dynamics of resistance evolution
- Combine experimental results with computational modelling of evolutionary dynamics to propose new therapeutic strategies for adaptive intervention.

Research proposal

Hypothesis: Drug resistance carries a fitness cost which can be exploited in new therapeutic strategies to direct cancer evolution

The student will generate data in the wet-lab to determine the cost of resistance in a large panel of cancer cell lines and patient derived organoids, treated with a broad range of standard-of-care chemotherapies.

We then intend to use our established methodology to barcode a panel of cancer cell lines in vitro, before treating them long-term with a range of clinically relevant chemotherapy drugs. At various intervals, cells will be removed for single cell DNA sequencing (to trace genetic lineages) and single cell RNA sequencing (to characterise the resistant phenotype). A suite of in vitro assays will be used to determine if resistant clones grow slower than their drug-sensitive counterparts, and map environmental dependence and potential mechanisms.

In the dry-lab, the student will lead mathematical and bioinformatic analysis on the sequencing data they have generated, refining and applying our existing mathematical framework (Whiting et al, 2025) to understand the evolutionary dynamics of resistance. By combining wet-lab and computational approaches, the student will determine the relationship between fitness costs and resistance mechanisms. Experiments will be replicated to determine under what conditions the resistant phenotype is reproducible, and therefore predictable. Finally the student will perform integrative analysis of all datasets to propose new therapeutic concepts for adaptive treatment.

The studentship will be based in the Genomics and Evolutionary Dynamics group, within the Centre for Evolution and Cancer. We are a highly diverse and interdisciplinary team of about 15 people, consisting of clinicians, biologists, mathematicians and computational scientists. Our lab has around 12 years of experience in both experimental and bioinformatic analyses of cancer evolution, and full training in both wet and dry lab techniques will be provided to the successful candidate.

To complement the core research, the candidate will benefit from targeted international secondments. At the University of Cambridge (with **Prof Jamie Blundell**) during months 19–20, the student will receive training in modelling clonal evolution in cancer. At Chalmers University (Gothenburg, with **Dr Eszter Lakatos**) in month 23, a two-week stay will provide complementary training in mathematical modelling. Finally, at the Centre for Genomic Regulation (Barcelona, with **Prof Manuel Irimia**) in month 24, a short secondment will focus on transcriptomic analyses in the context of protective cancer signatures and their relationship with resistance. These placements will ensure a strong interdisciplinary foundation, linking experimental, computational, and theoretical approaches.

Literature references

- **"A view on drug resistance in cancer"** Vasan et al, Nature. 2019 Nov;575(7782):299-309. doi: 10.1038/s41586-019-1730-1.
- **"Life history trade-offs in cancer evolution"** Aktipis et al, Nat Rev Cancer. 2013 Dec;13(12):883-92. doi: 10.1038/nrc3606.
- **"Adaptive therapy"** Gatenby et al, Cancer Res. 2009 Jun 1;69(11):4894-903. doi: 10.1158/0008-5472.CAN-08-3658.
- **"Adaptive Therapy Exploits Fitness Deficits in Chemotherapy-Resistant Ovarian Cancer to Achieve Long-Term Tumor Control"** Hockings et al. Cancer Res. 2025 Sep 15;85(18):3503-3517. doi: 10.1158/0008-5472.CAN-25-0351.
- **"Study protocol for Adaptive ChemoTherapy for Ovarian cancer (ACTOv): a multicentre phase II randomised controlled trial to evaluate the efficacy of adaptive therapy (AT) with carboplatin, based on changes in CA125, in patients with relapsed platinum-sensitive high-grade serous or high-grade endometrioid ovarian cancer"** Mukerjee et al. BMJ Open. 2024 Dec 22;14(12):e091262. doi: 10.1136/bmjopen-2024-091262.
- **"Quantitative measurement of phenotype dynamics during cancer drug resistance evolution using genetic barcoding"** Whiting et al, Nat Commun. 2025 Jun 20;16(1):5282. doi: 10.1038/s41467-025-59479-7.

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:	BSc (First or 2:1) or Master's degree, ideally in a quantitative subject (for example physics, mathematics, or computer science) but experience of cell or molecular biology is highly valued. A strong interest experimental cancer biology is essential, but prior wet-lab training is not essential. Experience with computational or mathematical modelling would be valuable. We are looking for a highly motivated candidate with the willingness to learn and an enthusiasm for tackling complex questions in evolutionary dynamics. A keen interest in how resistance evolves and how it can be managed is essential.
Intended learning outcomes:	- Wet-lab training in techniques for experimental evolution, for example tissue culture, proliferation assays, single cell sequencing. - Training in computational analysis of genomic data - In-depth training in modelling approaches (through placements at the University of

Cambridge (Prof Jamie Blundell) and Chalmers University (Dr Eszter Lakatos)).

- In-depth training in transcriptomic analyses (through a placement at the CRG in Barcelona (Prof Manuel Irimia))
- Structured training in core methodology: comparative omics, genetic diversity analysis, mathematical modelling, machine learning, and the use of model organisms (through the EvoMG doctoral network)
- Become an independent scientist, confident in hypothesis generation, experimental design and implementation
- Attain thorough knowledge of the subject area and associated literature, including critical review of research papers
- Training in scientific writing and presentation to large and diverse audiences

Advertising details

Project suitable for a student with a background in:

- ☒ Biological Sciences
- ☒ Physics or Engineering
- ☐ Chemistry
- ☒ Maths, Statistics or Epidemiology
- ☒ Computer Science