PhD Project Proposal

Funder details

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

Project details

Project title:	**Towards non-invasive monitoring and prediction of cancer evolutionary dynamics from cfDNA**

Supervisory team

Primary Supervisor:	**Prof Trevor Graham**
Associate Supervisor(s):	**Dr Annie Baker, Dr Ben O'Leary**
Secondary Supervisor:	**Prof Udai Banerji**

Divisional affiliation

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

Project background

Cancer development is fundamentally an evolutionary process, however monitoring evolutionary dynamics through treatment remains challenging. Our team have recently developed a new methodology that can monitor clonal evolution by measuring DNA methylation, a stably inherited epigenetic marker on tumour DNA (Gabbutt et al, 2022). The method analyses fluctuating CpG (fCpG) loci which oscillate between homozygous methylated, heterozygous, and homozygous demethylated states within individual cells. In a mixed population of cells we can detect clonal expansions by looking at the relative signal between these three states. We have recently applied this methodology to blood cancers, showing that we can infer clinically-relevant parameters such as tumour age and growth rate (Gabbutt et al, 2025). However the limited accessibility and sampling of solid tumours has so far limited its application in other cancer types.

Dying tumour cells shed fragments of their DNA into the bloodstream, and these can be detected as cell-free DNA (cfDNA) in plasma from cancer patients. Detection of specific tumour mutations (or indeed epimutations) in cfDNA is already used to monitor resistance and guide therapy (for example Sartore-Bianchi et al, 2022), however the (epi)genetic mutations that lead to cancer are diverse and most tumours share very few mutations, if any. Therefore we propose to instead use methylation profiles; these are maintained in cfDNA, and we hypothesise that they can be used to monitor tumour evolution non-invasively through liquid biopsies.

Major technical challenges to solve include dealing with low purity of tumour-derived cfDNA and the heterogeneous methylation patterns between different cell types.

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

- Develop a sequencing approach to detect mutations and methylation in cfDNA from cancer patients

- Build computational tools to interpret methylation profiles from cfDNA

- Use sequencing to reconstruct clonal dynamics through treatment and resistance

- Apply the new methodology to samples from large clinical cohorts

Research proposal

Hypothesis: Methylation profiling in cfDNA can be used to infer tumour clonal dynamics, for example in treatment response, resistance and recurrence.

The student will work closely with our our industrial partner **Nonacus**, to design the a panel for bisulphite sequencing of the selected methylation loci in cfDNA. Nonacus are experts in genomics technology for next-generation sequencing of liquid biopsies and will provide expertise in the panel design, manufacture and wet-lab protocol.

We will then apply the bespoke panel to the sequencing of cfDNA. We have an existing biobank of cfDNA from CRC patients, as well as cfDNA from people who don't have CRC. The student will need to develop a new computational pipeline for extracting the CRC-specific signal from a potentially low-purity cfDNA sample.

The student will then validate their pipeline by applying it to longitudinal cfDNA samples that we have biobanked in-house. Because the method doesn't analyse a patient-specific set of mutations, it should be widely applicable to any CRC cohort. Finally the student will apply it to large clinical cohorts that are readily accessible through our long-standing collaborations with clinicians at the Royal Marsden Hospital.

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 the development of novel sequencing approaches and bioinformatic analyses for cancer evolution, and full training will be provided to the successful candidate.

As part of their training the candidate will have the opportunity to visit two other institutions within the Doctoral Network. Firstly they will undertake a two-month placement at Chalmers University (Sweden, with **Dr Eszter Lakatos**), where they will be provided with training in mathematical modelling to facilitate the integration of cfDNA assays with models of clonal evolution in patients. Secondly the candidate will have a short two-week secondment at Barcelona Supercomputing Center (Spain, with **Dr Toni Gabaldón**), which will strengthen their ability to scale computational approaches to large datasets.

Literature references

- "**Fluctuating methylation clocks for cell lineage tracing at high temporal resolution in human tissues**" Gabbutt et al, Nat Biotechnol. 2022 May;40(5):720-730. doi: 10.1038/s41587-021-01109-w.

- "**Fluctuating DNA methylation tracks cancer evolution at clinical scale**" Gabbutt et al, Nature. 2025 Sep;645(8081):764-773. doi: 10.1038/s41586-025-09374-4

- "**Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial**" Sartore-Bianchi et al, Nat Med. 2022 Aug;28(8):1612-1618. doi: 10.1038/s41591-022-01886-0.

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 in a biological, computational or quantitative subject.
	A strong interest in evolutionary approaches to medicine is essential, and willingness to engage in extensive mathematical and computational work. Experience in sequencing technologies, epigenetics, or computational modelling would be highly advantageous but is not essential. Motivation to work at the interface of academia and industry, and enthusiasm for translational applications of genomics, will be highly valued.

Intended learning outcomes:

- Wet lab training in DNA extraction techniques and next generation sequencing (assay design, library preparation)

- Training in bioinformatic analysis

- In-depth training in mathematical modelling (through a two-month placement at Chalmers University in Gothenberg, Sweden with Dr Eszter Lakatos).

- 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