ICR The Institute of Cancer Research

PhD Project Proposal

Funder details	
Studentship funded by:	NIHR
Project details	
Project title:	**Development of the next generation circulating tumour DNA tests in gastrointestinal cancers**
Supervisory team	
Primary Supervisor:	Professor Michael Hubank
Associate Supervisor(s):	Professor Trevor Graham Dr Elizabeth Cartwright
Secondary Supervisor:	Professor Naureen Starling
Divisional affiliation	
Primary Division:	Cancer Biology
Primary Team:	Genomics and Evolutionary Dynamics
Site:	Sutton

Project background

Gastrointestinal cancers are often associated with poor prognosis and more limited treatment options when compared to other cancer types. Diagnosis can be difficult with limitations in acquiring a tissue diagnosis. Liquid biopsies are a simple blood test where tiny fragments of genetic material from a cancer can be detected known as circulating tumour DNA (ctDNA). ctDNA has the potential to revolutionise cancer diagnosis and treatment. It may allow for earlier diagnosis, detection of minimal residual disease (MRD), surveillance and monitoring treatment response or resistance. Moreover, ctDNA is being innovatively integrated into clinical trials as a novel biomarker and potential future surrogate for endpoints allowing for more expedient drug development.

In gastrointestinal cancers, current clinical utility of ctDNA is limited to genotyping of disease and detection of MRD with prognostic and some predictive indications in colorectal cancer (Benavides et al., 2022; Nakamura et al., 2024; Shah et al., 2025; Slater et al., 2024; Tie et al., 2022). Longitudinal monitoring of ctDNA may be important for patient outcomes. Evolutionary cancer biology suggests that continuous cancer treatment might accelerate drug resistance. Whilst initially effective, drugs fail by selecting for resistant cells while eradicating treatment sensitive cells. The resultant evolutionary “competitive release” permits resistant cells to rapidly proliferate, without competition from sensitive cells in the fight for limited cellular resources. CtDNA may provide a way to track this evolution. The current generation of ctDNA tests are prohibitively expensive, limiting their ability to be implemented for this use. There is a real need to develop quick, rapidly scalable assays. Nanopore technology may provide a possible solution through long read sequencing without the need for PCR amplification. Allowing for analysis of copy number change, methylation and potential reporting of single nucleotide variants in a more economical efficient test.

The project will perform analytical validation of emerging technologies including nanopore in ctDNA, clinically validated against a cohort of gastrointestinal cancer patients and understand evolutionary changes in gastrointestinal cancer changes through tracking ctDNA.

Project aims

- Analytical validation of the next generation of ctDNA test
- Utilisation of nanopore technology to create a cost effective efficient ctDNA test
- Clinical validation of an ultrasensitive ctDNA assay in an established biobank of clinical trial patients in both gastro-oesophageal cancer and pancreatic cancer
- Utilise ctDNA to understand the evolutionary biological changes of cancer from certain therapeutics.

Research proposal

The project will perform analytical validation of emerging technologies including nanopore in ctDNA, clinically validated against a cohort of gastrointestinal cancer patients and understand evolutionary changes in gastrointestinal cancer changes through tracking ctDNA.

This research project will drive the development of the next generation of circulating tumour DNA tests. ctDNA is poised to transform cancer care – offering faster, cheaper, and more precise tools for diagnosis, detection of MRD, monitoring, treatment and treatment resistance. The successful PhD candidate will collaborate with pre-eminent researchers in genomics and circulating tumour DNA, spanning lab innovation to clinical trial development and clinical implementation.

The PhD candidate will work on the following workstreams:

1. Analytical validation of the next generation of ctDNA test
Development of a low cost, efficient next generation circulating tumour DNA test that is easily scalable in all healthcare systems. This will include analytical validation of nanopore technology which offers the ability to directly sequence long read native DNA without PCR amplification. This enables simultaneous detection of various genomic and epigenic alterations including methylation patterns, copy number variants and single nucleotide variants in real time.

2. Clinical validation of the next generation of ctDNA tests in pancreatic and gastro-oesophageal cancer cohorts
The novel low cost ctDNA test will be clinically validated to determine sensitivity and specificity and overall assay performance in the following cohorts of patients:

<u>Pancreatic Cancer</u>
We have established a biobank of approximately 200 pancreatic cancer patients with accompanying blood, plasma, tissue and faecal specimens with correlating clinical data. Pancreatic cancer can be difficult to diagnose, especially in its early stages with technical limitations to obtaining a tissue diagnosis. Circulating tumour DNA offers a novel method to diagnose and monitor treatment response using a liquid biopsy.

<u>Gastro-oesophageal Cancer</u>
A subset of patients with advanced gastro-oesophageal adenocarcinoma are characterised by homologous recombination deficiency (HRD). The presence of HRD is known to convey PARP inhibitor sensitivity across numerous other tumour types. We have established a well characterised cohort of gastro-oesophageal patients treated with a PARP inhibitor, with corresponding HRD scoring, whole exome sequencing, RNA expression and multiplex immunofluorescent assessment of the tumour microenvironment as well as correlating clinical data.

3. Evaluating the evolution in gastro-oesophageal cancers treated with PARP inhibitors utilising a novel ctDNA test
Continuous cancer treatment might cause evolutionary changes that accelerates drug resistance. (Ingles Garces et al., 2023; Merlo et al., 2006). Through competitive release, cancer cells resistant to treatment may rapidly proliferate as sensitive cells no longer compete with them for resources. We have sequential plasma samples of a gastro-oesophageal cohort of patients treated with PARP inhibition. Using the novel ctDNA test that has been analytically and clinical validated, we will track and evaluate the evolution changes that occur in gastro-oesophageal cancer under treatment selection pressure with a PARP inhibitor.

Literature references

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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: Bachelor of Science

Intended learning outcomes:

- Familiarity with ctDNA biology, including origin, methylation, fragmentation patterns and clearance
- Familiarity with ctDNA detection methods (e.g. digital PCR, BEAMing, target sequencing), nanopore technology
- Awareness of sensitivity, specificity and clinical utility of liquid biopsies
- Ability to contribute to the design and optimisation of novel ctDNA platforms including nanopore technology
- Understanding of assay development, cost efficiency and scalability
- Proficiency in statistical analysis

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