PhD Project Proposal

Funder details

Studentship funded by:	MRC DTP iCASE – ICR and Merck

Project details

Project title:	Hyper-activation of oncogenic signalling to treat colorectal tumours

Supervisory team

Primary Supervisor:	Prof. Trevor Graham
Associate Supervisor(s):	Dr Frank Czauderna (Industry Supervisor) Dr Erica Oliveira (Associate ICR Supervisor) Dr Freddie Whiting (Associate ICR Supervisor) Dr Annie Baker (Associate ICR Supervisor)
Secondary Supervisor:	Prof Udai Banerji

Divisional affiliation

Primary Division:	Centre for Evolution and Cancer/Molecular Pathology
Primary Team:	Genomics and Evolutionary Dynamics lab
Site:	ICR Sutton

Project background

The concept of intentionally overactivating an oncogenic signalling as a treatment strategy has recently gained attention. In colorectal cancer, aberrant activation of Wnt signalling is a hallmark of the disease. However, it has been previously shown that inhibition of GSK3β, a negative regulator of Wnt-signalling, reduces cancer incidence (1-3). This shows that while aberrant Wnt signalling drives colorectal cancer, its overactivation can turn it into a liability. Cell plasticity has proven hard to study as it dynamically changes over time and needs to be distinguished from clonal evolution where cell phenotypes change because of selective pressure (4-6). In preliminary data, we have shown that colorectal cancer (CRC) cells that have evolved resistance to MAPK pathway inhibition are unable to tolerate WNT activation. This is exciting because it suggests cross-talk between oncogenic pathways that can be exploited in a new way by hyperactivation approaches.

Project aims

- **Data science.** We will construct machine learning methods to explore high throughput screening and patient data to identify negative regulators of oncogenic signalling in colorectal cancers that are potentially druggable.
- **Mathematical modelling** of signalling and evolutionary dynamics to identify plausible therapeutic windows.
- **Experimental *in vitro* validation** in preclinical models of hyperactivating agents.

Research proposal

WP1 – Leverage existing datasets to identify negative regulators of oncogenic signalling

- Explore the range of oncogenic signalling in healthy somatic cells to identify a 'healthy range' of pathway signalling (RNAseq analysis of GTEx).
- Look at oncogenic pathway activity as a function of mutations in the pathway to determine the physiological upper and lower bounds of oncogenic activity (RNAseq analysis of DepMap, BioGRID, OncoDB)
- Explore cell viability following experimental perturbation of oncogenic pathway components (and combinations of components) (DepMap)
- Seek to leverage existing high-throughput drug screening data from our industrial partner Merck to directly identify potential 'hyper-activating' compounds. We highlight that the novelty of the hyper-activating treatment approach means such compounds may have been overlooked in previous screens.

WP2 – Mathematical modelling of pathway signalling and evolutionary dynamics to identify potential hyper-activation therapeutic windows.

- Generate (stochastic branching process) models that combine our knowledge of signalling networks with evolutionary principles. Incorporate resistance mutations that change the basal level of cancer cell signalling.
- Within these models, pathway activity will also be modulated by simulating the action of drugs (and/or pathway perturbation) that target specific pathway components (leveraging results from WP1 and WP3).
- These models will enable us to predict combinations of treatments that maximise the time until treatment failure. To do this, we will use the mathematical toolkit of "optimal control theory".

WP3: Experimental Validation of Computational Predictions

- We will use functional assays in colorectal cancer cell lines and organoids to test the targets identified in WP1. These assays will help determine whether the identified negative regulators of oncogenic signalling are viable therapeutic targets. By measuring cell viability and protein activity, we will assess whether hyper-activating these pathways effectively reduces cancer cell survival. Based on the targets, we will explore the best approach for pathway inhibition including RNAi, dTAG and the repurpose of existing drugs.

- To further validate the role of negative regulators, the team will use genetic modification techniques, such as Tet-on and Tet-off systems, and drugs already available to modulate the expression of these regulators in cancer cells. This approach allows precise temporal control over the levels of pathway activity, making it possible to explore how different levels of signalling affect cancer cell fitness. The ability to fine-tune pathway activity is critical for validating the hyper-activation strategy

and understanding its effects on cell survival. Our preliminary data shows that the WNT activator CHIR99021 is cytotoxic both in naïve and resistant CRC cells; this will be further explored.

Overall Goals and Impact

The studentship will provide interdisciplinary research experience, combining bioinformatic, theoretical, and experimental approaches. The three work packages are designed to complement each other, with WP1 providing data-driven insights into pathway regulation, WP2 using mathematical models to predict optimal treatment strategies, and WP3 experimentally validating those predictions in cancer cells.

The project aligns with the Advanced Therapeutics DTP research theme and aims to combine academic research with industrial expertise. Collaborating with Merck offers the opportunity to explore existing drug development data to identify (and repurpose) existing agents that cause oncogenic hyper-activation, and to facilitate rapid translation of findings.

Ultimately, we hope to develop a radical new paradigm for cancer treatment.

Literature references

1. Ito, T., Young, M.J., Li, R., et al., 2021. Paralog knockout profiling identifies DUSP4 and DUSP6 as a digenic dependence in MAPK pathway-driven cancers. *Nature Genetics*, 53, pp.1664–1672. doi: 10.1038/s41588-021-00967-z.
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4. Javier Fernandez-Mateos, Salvatore Milite, Erica Oliveira, Georgios Vlachogiannis, Bingjie Chen, Erika Yara, George D Cresswell, Chela James, Lucrezia Patruno, Gianluca Ascolani, Ahmet Acar, Timon Heide, Inma Spiteri, Alex Graudenzi, Giulio Caravagna, Trevor Graham, Luca Magnani, Nicola Valeri, Andrea Sottoriva. Epigenetic heritability of cell plasticity drives cancer drug resistance through one-to-many genotype to phenotype mapping. bioRxiv 2023.11.15.567140.
5. Whiting FJH, Household J, Baker AM, Sottoriva A, Graham TA. Phenotypic noise and plasticity in cancer evolution. Trends Cell Biol. 2024 Jun;34(6):451-464.
6. Calum Gabbutt, Martí Duran-Ferrer, Heather Grant, Diego Mallo, Ferran Nadeu, Jacob Household, Neus Villamor, Olga Krali, Jessica Nordlund, Thorsten Zenz, Elias Campo, Armando Lopez-Guillermo, Jude Fitzgibbon, Chris P Barnes, Darryl Shibata, José I Martin-Subero, Trevor A Graham. Evolutionary dynamics of 1,976 lymphoid malignancies predict clinical outcome.

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 or equivalent in biological or physical sciences with First or 2:1. MSc preferred. Candidates will have substantial experience of at least one, and ideally all, of the following: experimental models, mathematical modelling and data science.

Intended learning outcomes:	• Experience of interdisciplinary cancer research, and industry collaboration • Knowledge of cancer evolution • Experience of cancer genomics • Skills in mathematical biology • Knowledge of pharmacodynamic and pharmacokinetic data • Skills in tissue culture and in vitro modelling • Experience of working with clinical cancer datasets

Advertising details

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