The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by: ICR

Project details

Project title: Studying the emerging role of diet and nutrition in cancer prevention and therapy response

Supervisory team

Primary Supervisor: Dr George Poulogiannis

Associate Supervisor(s): NA

Secondary Supervisor: Prof. Montserrat García-Closas

Divisional affiliation

Primary Division: Cancer Biology

Primary Team: Signalling & Cancer Metabolism

Site: Chelsea

Project background

Dietary intake has long been presumed to influence cancer initiation, progression, and therapy response [1-3]. However, rigorous clinical evidence supporting the effectiveness of alternative diets alone in treating or preventing cancer is still lacking. This proposal aims to (i) identify and mechanistically interrogate the metabolic and signalling pathways affected by different dietary interventions, and (ii) integrate the genetic, metabolic and environmental information to optimise metabolic responses to diet with the ultimate goal to tailor dietary approaches for the prevention and treatment of PI3K/AKT-active breast tumours.

Previous work from our lab has shown that several unconnected components of PI3K/AKT signalling converge on cPLA2 activation and enhanced metabolism of the omega-6 polyunsaturated fatty acid, arachidonic acid (AA) (Koundouros et al., 2020). Both genetic and pharmacological (ASB14780) inhibition of cPLA2 significantly impaired the growth of *PIK3CA*-induced tumourigenicity *in vitro* and *in vivo*, and this effect was more prominent under exogenous fatty acid-free conditions, alleviating any compensatory mechanisms to obtain AA. On the contrary, the addition of the ketogenic diet, a high-fat, low-carbohydrate diet with adequate amounts of protein, has shown to increase the efficacy of PI3K/AKT-active cancers to PI3K inhibition by preventing the insulin feedback induced by PI3K inhibitors (Hopkins et al., 2018). However, in some instances, such as the acute myeloid leukaemia (AML) model, the ketogenic diet alone was shown to accelerate disease progression, suggesting that this diet could have other implications beyond suppressing insulin feedback, highlighting the need for further investigation about the emerging role of diet in cancer prevention and therapy response.

Project aims

This project focuses on gaining a mechanistic understanding on the role of different dietary interventions in the prevention and therapy response of PI3K/AKT-altered tumours. We propose to address the following Aims:

- **Aim 1. Deconstruct the signalling and metabolic signatures associated with different dietary and nutrient interventions.**
- **Aim 2. Targeting metabolic vulnerabilities of breast cancers with PI3K/Akt activation through "drug and diet" combinations**

Research proposal

Our hypothesis is that cancers with constitutive activation of the PI3K/AKT pathway conferred by loss of PTEN or activating mutations in *PIK3CA* have a number of metabolic Achilles heels that can be targeted directly by distinct dietary interventions. Mechanistic exploration of the metabolic and signalling restructurings conferred by these interventions, when given alone or in combination with PI3K/AKT-pathway therapies, can assist with pairing the right diet with the right patient, representing a significant step forward in precision nutrition for the prevention and treatment of PI3K/AKT-active tumours.

The first objective of this study will be to identify specific metabolite and signalling profiles associated with the exposure of PI3K/AKT-active cancers to different dietary interventions (e.g. ketogenic, low-glycaemic, and/or ketogenic diets supplemented with different omega 6/3 ratio). This will be achieved by performing mass-spec metabolomics profiling of treated and not-treated patient-derived xenograft and organoid models followed by extensive signalling profiling with the focus to unveil novel dietary interventions-metabolic phenotype interactions.

We will also assess how do different dietary interventions affect PI3K/AKT-driven tumour growth, as well as blood glucose, insulin, blood triglycerides and inflammatory markers.

The second aim of this project is to identify metabolic vulnerabilities of breast cancers with PI3K/Akt activation that can be exploited through diet alone or drug and diet combinations. These will be based on the mechanistic exploration of key signalling events induced by the different diets and studying whether they are dictated by lipid phosphatase/kinase and Akt-dependent and independent functions. This work will uncover and biochemically dissect the signalling nodes that contribute in the metabolic restructurings of PI3K/Akt activated cancers and identify novel metabolic vulnerabilities both in terms of modifying tumour diet alone or in combination with inhibition of co-dependent pathways. Such therapeutic interventions will be tested across representative PDO and PDX models with or without PTEN loss or oncogenic *PIK3CA* mutations.

This project will deliver insight into major questions that are applicable across cancer research and precision medicine. We will establish the broader metabolic and signalling wiring of PI3K/AKT-driven breast cancers induced by different dietary interventions and better determine the plasticity of the tumour metabolism across a variety of pre-clinical models. We will identify the metabolic vulnerabilities imposed by dietary intake and elucidate the metabolic biomarkers that govern the response to dietary interventions when given alone or in combination with known therapeutic regimes. In doing so, we will establish the pivotal systemic metabolic changes associated with tumour initiation, progression and response to treatment. These results will be the cornerstone of designing clinical trials capable of treating a substantial fraction of cancer patients.

Literature references

1. Taylor, S.R., et al., *Developing dietary interventions as therapy for cancer.* Nat Rev Cancer, 2022. **22**(8): p. 452-466.
2. Altea-Manzano, P., et al., *Nutrient metabolism and cancer in the in vivo context: a metabolic game of give and take.* EMBO Rep, 2020. **21**(10): p. e50635.
3. Tajan, M. and K.H. Vousden, *Dietary Approaches to Cancer Therapy.* Cancer Cell, 2020. **37**(6): p. 767-785.

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, or be on track to receive, a First- or Upper Second- class Honours degree (or a Masters) in **Biochemistry, Cell Biology or equivalent** , have experience in **tissue culture and molecular biology techniques (e.g. RNA/protein analyses)**, and must have a basic knowledge of **the role of metabolism in cancer**. Experience in some of the areas mentioned in the project description (e.g. breast cancer, organoids, metabolomics) is highly desirable and willingness to work with laboratory mice during the duration of the PhD is an essential requirement.

Intended learning outcomes:

- Attain a thorough knowledge of the literature and a comprehensive understanding in the area of precision nutrition and cancer metabolism.
- Be able to demonstrate originality in the application of targeting tumour metabolism.
- Learn how to perform label free and stable isotope-assisted metabolomics and acquire expertise in the development and use of *in vitro 3D* and *in vivo* pre-clinical models.
- Gain skills in bioinformatics and data analysis.
- Acquire proficiency in acting autonomously in the planning and implementation of research, as well as working as part of a team.
- Gain oral presentation and scientific writing skills.

Advertising details

Project suitable for a student with a background in:

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