ICR The Institute of Cancer Research

UKRI Medical Research Council

PhD Project Proposal

Funder details

Studentship funded by:	MRC iCASE (Artios)

Project details

Project title:	Identifying therapeutical opportunities within replicative stress response pathways for the development of novel therapeutic strategies to treat cancer

Supervisory team

Primary Supervisor:	Wojciech Niedzwiedz
Associate Supervisor(s):	Özgün Özer (Artios) Eeson Rajendra (Artios) Ronan Broderick
Secondary Supervisor:	Sebastian Guettler

Divisional affiliation

Primary Division:	Cancer Biology
Primary Team:	Genome Instability and Cancer
Site:	Chelsea

Project background

Alternative Lengthening of Telomeres (ALT) allows cancer cells to achieve unlimited replicative potential by preserving their telomeres in the absence of telomerase. ALT is employed by 10-15% of cancers and is associated with mesenchymal and neuroepithelial tumours. Currently, no useful therapies exist for the treatment of ALT-reliant tumours since the exact molecular mechanisms of the ALT pathway are not fully understood.

This PhD programme aims to characterise the early molecular events that allow cancer cells to initiate a productive ALT-dependent telomere maintenance. In addition, the candidate will utilise CRISPR-CAS9 based whole genome screens to identify novel synthetic lethal combinations to specifically target ALT-reliant tumours.

Research proposal

The architecture of our genome presents many obstacles to the replication machinery, containing many evolutionarily conserved loci that are comprised of tandem repeat arrays, such as the centromere, rDNA repeats, common fragile sites, trinucleotide repeat expansions and telomeric repeat sequences [1, 2]. Failure to accurately replicate these regions leads to chromosome breakage and tandem repeat expansions, which underlie a myriad of human diseases including cancers.

Replication of telomeric sequences at chromosome ends presents a unique set of problems that the cell must overcome i.e., (i) telomeric DNA is comprised of tandem repeat sequences (arrays of TTAGGG), which are bound to

and protected by the shelterin complex via the formation of a “T-loop” structure, which can act as “replication barriers” and (ii) due to the semi-conservative nature of DNA replication and the structure of chromosome ends, cells encounter the so-called “end-replication problem”, which is defined as an inability of the DNA replication machinery to mature the final Okazaki fragment. The former results in replication fork stalling/collapse, the latter is associated with shortening of telomeric sequences each time the cell divides. This is important from clinical perspective as telomere shortening limits the amount of times cell division can take place, thereby preventing cell immortalisation. Consequently, in order to immortalise, cancer cells need to elongate and maintain their telomeres. This is mediated by two distinct pathways. The major one relies on re-expression of the Telomerase enzyme, which mediates telomere elongation via a reverse transcriptase-based mechanism. However, 10-15% of cancers employ the ALT pathway (Alternative Lengthening of Telomeres) to maintain their telomeres, and this mechanism is highly prevalent in mesenchymal and neuroepithelial tumours associated with poor prognosis (3). How cells initiate efficient ALT at telomeres is poorly understood.

Thus, the primary aim of this PhD project will be to comprehensively delineate the mechanisms of repair pathways essential for the survival of ALT-dependent cancers using state-of-the art cell biology and microscopy approaches.

During the course of the project, the student will become proficient in a broad range of techniques, including CRISPR-Cas9 genome editing, super-resolution fluorescence microscopy, single molecule analysis of DNA replication, bioinformatics and proteomics. The student will be encouraged to attend and present their work at national and international meetings, and to be involved in organizing and presenting at journal clubs and internal seminar series.

Literature references

[1] Kass, E. M., Moynahan, M. E. & Jasin, M. When Genome Maintenance Goes Badly Awry. Mol Cell 62, 777-787, (2016).
[2] Zeman, M. K. & Cimprich, K. A. Causes and consequences of replication stress. Nat Cell Biol 16, 2-9, (2014).
[3] Jerry W Shay, Woodring E Wright. Telomeres and telomerase: three decades of progress. Rev Genet 20(5):299-309, (2019).

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 sciences or medicine
Intended learning outcomes:	The successful applicant will learn how to: • Plan and design properly controlled scientific experiment, informed by relevant literature. • Obtain a working knowledge of cutting edge molecular biology techniques such as CRISPR/Cas9 genome editing, qPCR, confocal and super resolution fluorescent microscopy, flow cytometry etc. • Employ state of the art microscopy techniques including the analysis of fluorescently tagged proteins expressed in human cells. • Gain skills in oral presentation, with data generated presented at national and international conferences. • Exposure to Artios’ assays and high throughput/high content imaging platform.

Advertising details

Project suitable for a student with a background in:

- [x] Biological Sciences
- [ ] Physics or Engineering
- [ ] Chemistry
- [ ] Maths, Statistics or Epidemiology
- [ ] Computer Science