PhD Project Proposal

Funder details

Studentship funded by:	MRC iCASE (Tesselate)

Project details

Project title:	Developing new therapeutic strategies for ALT positive sarcomas

Supervisory team

Primary Supervisor:	Paul Huang
Associate Supervisor(s):	Katie Chapman (Tessellate)
Secondary Supervisor:	Chris Lord

Divisional affiliation

Primary Division:	Molecular Pathology
Primary Team:	Molecular and Systems Oncology
Site:	Sutton

Project background

Alternative lengthening of telomeres (ALT) is a telomere maintenance mechanism (TMM) that engages homology directed repair pathways to extend telomeres in cancer cells. ALT is enriched in cancers of mesenchymal or neuroepithelial origin such as sarcomas, gliomas and neuroblastoma. For instance, in soft tissue sarcomas (STS) such as leiomyosarcomas (LMS) and undifferentiated pleomorphic sarcomas (UPS), up to 60% of patients have been found to be ALT positive. ALT positivity is associated with increased tumour size, high mitotic index and poor prognosis in these patients. There is a heterogeneity of ALT mechanisms in STS including predominantly ATRX loss. Despite a dependency on this TMM in a significant proportion of cancer patients, there is currently a lack of therapies that selectively target ALT-positive cancers. In this project, we will use STS as a model system and employ a combination of Omics analysis and high-content image-based screens in a unique panel of patient-derived models to identify emerging drug targets in the DNA damage response and replication stress pathways that are selective for ALT-positive cancers.

Project aims

- Identify biological pathways and drug targets that are enriched in ALT-positive sarcomas from Omic datasets
- Evaluate the efficacy and selectivity of drugs that target DNA damage response and replication stress regulation pathways in ALT-positive sarcomas
- Evaluate the heterogeneity of drug response and its association with ALT positivity at single cell level

Research proposal

Aim 1: Deep mining of Omic datasets for targetable signalling pathways in ALT-positive STS.

The student will assess the ALT status (by C-circle assay and Telo-FISH analysis) in tumour specimens from sarcoma patients that have undergone comprehensive Omics profiling in the Huang laboratory. Bioinformatic analysis will be then employed to identify molecular pathways and drug targets that are enriched in ALT-positive STS. Candidate drug targets identified in Aim 1 will be functionally tested in Aim 2.

Aim 2. High-content imaging screens of candidate drug targets in ALT-positive patient-derived models.

By mining the literature, we have identified a targeted panel of well-established and emerging small molecule inhibitors in the DNA damage response and replication stress regulation pathways that may have efficacy in ALT-positive cancers. This will be fortified with additional drug targets identified from the patient-level Omic data in Aim 1. In this aim, we will high-content imaging to evaluate, at single cell resolution, 1. The heterogeneity of drug responses and 2) the association of drug response to ALT status These screens will be done in collaboration with Tessellate Bio in a panel of in-house patient-derived and commercial LMS cell line models from the Huang Lab.

Aim 3. Rational evaluation of selected candidate drugs agents in vivo.

Drug candidates from Aim 2 that are found to be most selective for ALT-positive cells will be evaluated in vivo. The best strategies arising from the high content screens will be evaluated in a subset of the Huang Lab's unique collection of patient-derived LMS and UPS xenograft models to test the validity of our findings in vivo. By comparing the drug effects in ALT-positive and ALT-negative xenograft models, we will be able to 1. Establish the selectivity of these drugs for ALT status and 2. Determine which biomarker(s) would be the best candidate for stratifying patients to these drugs.

Literature references

[1] Chudasama et al., Integrative genomic and transcriptomic analysis of leiomyosarcoma. Nat Commun. 2018 Jan 10;9(1):144. doi: 10.1038/s41467-017-02602-0

[2] Gao & Pickett. Targeting telomeres: advances in telomere maintenance mechanism-specific cancer therapies. Nat Rev Cancer. 2022 Sep;22(9):515-532. doi: 10.1038/s41568-022-00490-1.

[3] Liau et al., Comprehensive screening of alternative lengthening of telomeres phenotype and loss of ATRX expression in sarcomas. Mod Pathol. 2015 Dec;28(12):1545-54. doi: 10.1038/modpathol.2015.114

[4] Lawler et al., Alternative lengthening of telomeres (ALT) influences survival in soft tissue sarcomas: a systematic review with meta-analysis. BMC Cancer. 2019 Mar 14;19(1):232. doi: 10.1186/s12885-019-5424-8.

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 a First or 2:1 Honours degree or a Masters in biology/ biochemistry/ cancer biology or a related discipline. Academic knowledge in cancer biology, cell biology, or molecular biology. Previous laboratory experience. Good presentation and communication.
Intended learning outcomes:	• Knowledge in cancer biology (ALT and DNA damage response), high content screening, Omics data analysis, translational cancer research, drug discovery, molecular pathology • Experimental skills in biochemical, high content imaging screens, bioinformatics analysis and preclinical in vitro and in vivo models • Ability to design, manage and progress a defined scientific project

- Scientific writing, presenting and communication skills. Ability to read and process relevant literature.
- Appreciation for the interface between academic and industrial research and the key steps required for drug discovery and getting a drug to market

Advertising details

Project suitable for a student with a background in:

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