The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Title:	TRANS-CASPS: Translational studies in the Cediranib in Alveolar Soft Part Sarcoma (CASPS) trial.

SUPERVISORY TEAM	
Primary Supervisor(s):	Dr Robin Jones
Backup Supervisor:	Dr Paul Huang
Lead contact person for the project:	Dr Robin Jones
DIVISIONAL AFFILIATION	
Primary Division:	Clinical Studies
Primary Team:	Sarcoma Clinical Trials

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Alveolar soft part sarcoma (ASPS) is a rare form of sarcoma with poor long-term outlook. Cediranib is a multi-target tyrosine kinase inhibitor (TKI) that has been clinically evaluated for the treatment of selected soft tissue sarcoma (STS) histological subtypes such as ASPS. The CASPS trial is a double blind, placebo-controlled randomised trial of the anti-angiogenic agent cediranib in ASPS. A proportion of patients showed a clinical response to this drug but the mechanisms of drug action are unclear. In addition, there are patients who display intrinsic resistance to this drug while those who do respond eventually develop acquired resistance. There is currently a poor understanding of the mechanistic determinants of cediranib resistance which hinders the development of predictive biomarkers and therapeutic strategies to overcome resistance.

The project seeks to address these questions by experimentally defining the molecular mechanisms of cediranib response and resistance in ASPS. The overarching objective is to undertake translational studies that employ molecular profiling to characterise tissue and blood specimens collected in the CASPS trial. By assessing the baseline and dynamic molecular alterations associated with therapy response, this approach will define targets of drug action and lead to the characterisation of candidate mechanisms that drive cediranib resistance in ASPS. It is anticipated that this research will accelerate the discovery of innovative biomarkers for patient stratification as well as salvage or combination therapies to achieve durable treatment responses and ultimately improve ASPS patient outcomes.

PROJECT AIMS

- Molecular profiling of tissue specimens to define response and resistance mechanisms associated with cediranib treatment in ASPS.
- Develop liquid biopsies with the goal of developing non-invasive early detection assays for monitoring drug response.

- Identify candidate therapeutic strategies for overcoming cediranib resistance in ASPS.
- Characterising the tumour microenvironment in ASPS and determine its link with cediranib response

RESEARCH PROPOSAL

Cediranib is a multi-target tyrosine kinase inhibitor (TKI) that exhibits selectivity for a spectrum of receptor tyrosine kinases (RTKs). It has been clinically evaluated for the treatment of selected soft tissue sarcoma (STS) histological subtypes, including alveolar soft part sarcoma (ASPS). In addition to inhibiting VEGFR-mediated angiogenesis, direct inhibition of tyrosine kinase signalling in tumour cells is likely to also contribute to its clinical efficacy. A recent Phase II randomised placebo controlled study of cediranib in ASPS patients (the CASPS study) demonstrated that a significant proportion of patients show a clinical response to this drug. However there are still several important questions that remain to be answered which will be the focus of this studentship: 1. What are the molecular targets of this drug in ASPS? 2. What are the mechanisms of drug resistance and can we identify therapies that could overcome or prevent such resistance from developing and 3. What are the biomarkers of response and resistance to cediranib and can we develop strategies for early detection of drug response?

This studentship aims to address these questions by defining the molecular mechanisms of cediranib response and resistance in ASPS. In this translational research project, the successful applicant will analyse clinical material (tissue and bloods) from the CASPS study to define the mechanisms of cediranib action in ASPS.

The project is composed of 3 aims.

Aim 1: Define candidate molecular mechanisms of cediranib resistance and sensitivity in ASPS using state-of-the-art molecular profiling approaches (RNAseq, methylation analysis and proteomic profiling by mass spectrometry).

Aim 2: Develop liquid biopsies for monitoring cediranib response and disease relapse using serial blood samples from the CASPS trial, including circulating endothelial cell profiling and cytokine analysis.

Aim 3: Characterise the tumour microenvironment (immune, inflammatory and matrisome) in ASPS specimens from the CASPS trial using immunohistochemistry, RNASeq and proteomic analysis.

Training and development

The PhD student will be supervised by Dr Robin Jones, Head of the Sarcoma Unit at the Royal Marsden and will benefit from mentorship and training from multi-disciplinary team in Dr Paul Huang's laboratory within the Division of Molecular Pathology. There will be a close collaboration with the Chief Investigator of the CASPS trial Prof Ian Judson and other research teams at the ICR (Prof. Nick Turner, Dr. Rachael Natrajan and Dr. Yinyin Yuan). The student will be trained in state-of-the-art Omic profiling strategies as well as the latest liquid biopsy analysis techniques. The student will be exposed to Translational research, Sarcoma Molecular Pathology, Cancer Biology, Signal Transduction and Systems Pharmacology.

We anticipate that this PhD project will address an existing knowledge gap in our understanding of anti-angiogenic TKI responses in ASPS and have a direct impact on improving patient outcomes by delivering new strategies to overcome drug resistance and achieve durable therapy responses in patients.

LITERATURE REFERENCES

1. Judson, I., et al., Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial. Lancet Oncology 2019. 20(7): p. 1023-34.

2. Ladanyi, M., et al., *The der(17)t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25.* Oncogene, 2001. **20**(1): p. 48-57.

3. Lazar, A.J., et al., *Angiogenesis-promoting gene patterns in alveolar soft part sarcoma.* Clin Cancer Res, 2007. **13**(24): p. 7314-21.

4. Ishiguro, N. and H. Yoshida, *ASPL-TFE3 Oncoprotein Regulates Cell Cycle Progression and Induces Cellular Senescence by Up-Regulating p21.* Neoplasia, 2016. **18**(10): p. 626-635.

5. Sleijfer, S., et al., *Cytokine and angiogenic factors associated with efficacy and toxicity of pazopanib in advanced soft-tissue sarcoma: an EORTC-STBSG study.* Br J Cancer, 2012. **107**(4): p. 639-45.

6. Lewin, J., et al., *Response to Immune Checkpoint Inhibition in Two Patients with Alveolar Soft-Part Sarcoma.* Cancer Immunol Res, 2018. **6**(9): p. 1001-1007.

7. Somaiah, N., et al., *A phase II multi-arm study to test teh efficacy of durvalumab and tremelimumab in multiple sarcoma subtypes.* Connective Tissue Oncology Society (CTOS) 2017 Annual Meeting, 2017.

8. Wilky, B.A., et al., *Antitumor activity of axitinib plus perbrolizumab in a phase II trial for patients with advanced alveolar soft part sarcoma (ASPS) and other soft tissue sarcoma.* Connective Tissue Oncology Society (CTOS)

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: e.g. BSc or equivalent in specific subject area(s)	Candidates must have a first class or upper second class honours BSc Honours/MSc in Biology, Biochemistry, Cancer Biology or a related discipline.
Intended learning outcomes:	• Knowledge in sarcoma biology, signal transduction, cancer therapeutics • Experimental skills in biochemical, molecular biology and genomics/proteomic techniques • Liquid biopsy analysis • Ability to design, manage and progress a defined scientific project • Scientific writing, presenting and communication skills. Ability to read and process relevant literature.

ADVERTISING DETAILS

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

	☐ Computer Science ☐ Other (provide details)
Keywords:	**1. Sarcoma**
	2. Translational Research
	3. Molecular Profiling
	4. Kinase inhibitors
	5. Liquid biopsies
	6. Drug resistance