The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL

PROJECT DETAILS	
Project Title:	Defining biomarkers and mechanisms of cediranib response in sarcoma

SUPERVISORY TEAM	
Primary Supervisor(s):	Dr Paul Huang
Other supervisory team members:	Dr Robin Jones
Lead contact person for the project:	Dr Paul Huang

DIVISIONAL AFFILIATION	
Primary Division:	Molecular Pathology
Primary Team:	Protein Networks Team

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

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 alveolar soft part sarcoma (ASPS). A proportion of patients show 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.

This studentship seeks 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 utilise clinical material (tissue and bloods) from a randomised placebo controlled Phase II trial of Cediranib in ASPS to identify targets of drug action, develop predictive biomarkers for drug response and characterise mechanisms of drug resistance.

PROJECT AIMS

- Molecular profiling of tissue specimens to define response and resistance mechanisms associated with cediranib treatment.
- Discover circulating biomarkers for drug response with the goal of developing non-invasive early detection assays for monitoring drug response.
- Develop therapeutic strategies for overcoming cediranib resistance in ASPS.

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 biomarkers of response and resistance to cediranib and can we develop strategies for early detection of drug response? 2. What are the molecular targets of this drug in ASPS? And 3. What are the mechanisms of drug resistance and can we identify therapies that could overcome or prevent such resistance from developing.

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 biomarkers and mechanism of cediranib response in sarcoma.

The project is composed of 3 aims.

Aim 1: Define the molecular alterations associated with good and poor responders to cediranib using state-of-the-art molecular profiling approaches (DNA, RNA and protein profiling).

Aim 2: Identify candidate circulating biomarkers for the development of non-invasive early detection assays of drug response

Aim 3: Characterise mechanisms of drug resistance and develop candidate therapeutic strategies to overcome resistance.

Training and development

The PhD student will be integrated into the multi-disciplinary Protein Networks Team in the Division of Molecular Pathology. The student will benefit from mentorship and training from other members of the Huang laboratory within a collaborative and supportive environment. There will be a close collaboration with the Sarcoma Unit led by Dr. Robin Jones as well as the Chief Investigator of the CASPS trial Prof Ian Judson. The student will be trained in molecular biology techniques as well as gain hands-on experience in molecular profiling strategies. The student will be exposed to Cancer Biology, Signal Transduction, Systems Pharmacology and Sarcoma Molecular Pathology.

LITERATURE REFERENCES

Judson et al., Phase II study of cediranib in patients with advanced gastrointestinal stromal tumours or soft tissue sarcoma. Clin Cancer Res 2014, 20(13):3603-12

Kummar et al., Cediranib for metastatic alveolar soft part sarcoma. J Clin Oncol. 2013, 31(18):2296-302.

Folpe and Deyrup., Alveolar soft-part sarcoma: a review and update. J Clin Pathol. 2006 59(11):1127-32.	
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 or 2:1 Honours degree or a Masters in a relevant discipline. • Academic knowledge in cancer biology and molecular biology • Previous laboratory experience • Good presentation and communication skills
Intended learning outcomes: Please provide a bullet point list (maximum of seven) of the knowledge and skills you expect the student to have attained on completion of the project.	• Knowledge in sarcoma biology, signal transduction, cancer therapeutics • Experimental skills in biochemical, molecular biology and genetic/proteomic techniques • Ability to design, manage and progress a defined scientific project • Scientific writing, presenting and communication skills. Ability to read and process relevant literature.