The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL

PROJECT DETAILS	
Project Title	TRANS-TAPPAS: Translational studies in the TAPPAS (TRC105 and pazopanib versus pazopanib alone in patients with advanced angriosarcomas) trial
Short Project Title	**Translational studies in the TAPPAS trial**

SUPERVISORY TEAM	
Primary Supervisor	Paul Huang
Associate Supervisor(s)	Robin Jones

DIVISIONAL AFFILIATION	
Primary Division	Molecular Pathology
Primary Team	Molecular & Systems Oncology Team
Site	Sutton

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

AS is an aggressive rare sarcoma subtype with a poor long-term outlook for patients with incurable advanced or metastatic disease (< 1 year). Current options are limited with chemotherapy being the mainstay of palliation and other systemic therapies having little durable impact on the disease course. The anticancer drug pazopanib and the therapeutic antibody TRC105 both target the formation and maintenance of blood vessels, and it is from the uncontrolled growth of these blood vessel cells that AS develops. The combination of pazopanib and TRC105 versus treatment with pazopanib alone have recently been assessed in the TAPPAS (TRC105 and pazopanib versus pazopanib alone in patients with advanced angiosarcomas) clinical trial. Despite being terminated early for futility, there was a subset of patients within this trial who showed durable clinical benefit, suggesting heterogeneity within this disease. Poor understanding of this observed heterogeneity presents a key obstacle to the development of effective ways to stratify AS patients and optimise treatment selection. Research specimens from this largest trial in AS offer an unprecedented opportunity to address these challenges.

The objective of this project is to perform translational studies comprising deep molecular analysis of tissue specimens and blood samples from TAPPAS. The student will uncover the biological and immunological features that can predict which are the AS patients most likely to benefit from drug treatment. Such a predictive tool will help doctors administer these drugs to the right patients while sparing those patients who are unlikely to benefit from unnecessary side effects. We will also determine if liquid biopsies can be used to monitor early treatment response in a non-invasive manner which would minimise the need for tissue biopsies. We anticipate that this research will accelerate the discovery of innovative biomarkers for patient stratification and uncover therapeutic opportunities which will ultimately improve patient outcomes.

PROJECT AIMS

- **Define the molecular features and immune landscape of AS patients to better understand the biological mechanisms underlying therapy response and resistance**
- **Validate in-house biomarker panels and develop new candidate biomarkers for anti-angiogenic therapy response**
- **Assess circulating biomarkers as a means to monitor therapy response in blood samples**

RESEARCH PROPOSAL

Given that AS arises from the vascular endothelium, there is rationale for the use of anti-angiogenic agents such as pazopanib (PZP) in this disease. Endoglin is a co-receptor for TGFβ which is overexpressed in AS and endoglin blockade leads to preclinical anti-tumour activity. Given that the endoglin expression in AS cells is increased following inhibition of angiogenic factors, there is a basis for exploiting the combination of anti-angiogenic therapies (e.g. PZP) together with anti-endoglin agents. TAPPAS is an international multi-centre randomised phase III trial (NCT02979899) which compared TRC105 (anti-endoglin antibody) and PZP versus PZP alone in patients with advanced AS. Although the trial was terminated due to the lack of benefit of the combination versus PZP alone, a subset of patients in the combination arm were found to have durable PFS benefit. This result highlights an underlying heterogeneity in AS, with the majority of the study cohort harbouring resistance to PZP or the combination, but with the combination showing activity in a select proportion of AS patients.

This studentship aims to address these questions by defining the molecular mechanisms of pazopanib and TRC105 response and resistance in AS. In this translational research project, the successful applicant will analyse clinical material (tissue and bloods) from the TAPPAS study to define the mechanisms of drug action in AS.

The project is composed of 3 aims.

Aim 1: Define candidate molecular mechanisms of pazopanib and TRC105 resistance and sensitivity in AS using state-of-the-art molecular profiling approaches (transcriptomics and proteomic profiling by mass spectrometry).

Aim 2: Develop liquid biopsies for monitoring pazopanib and TRC105 response and disease relapse using serial blood samples from the TAPPAS trial, including circulating cytokine analysis.

Aim 3: Characterise the tumour immune microenvironment in AS specimens from the TAPPAS trial using multi-spectral immunofluorescence.

Training and development

The PhD student will be supervised by Dr Paul Huang in the Division of Molecular Pathology and will benefit from mentorship and training in multi-disciplinary team. There will be a close collaboration with the Chief Investigator of the TAPPAS trial Prof Robin Jones, Head of the Sarcoma Unit at the Royal Marsden. The student will be trained in state-of-the-art Omic profiling strategies as well as 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 drug responses in AS 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

Jones, R. L. *et al.* 1667O Results of the TAPPAS trial: An adaptive enrichment phase III trial of TRC105 and pazopanib (P) versus pazopanib alone in patients with advanced angiosarcoma (AS). *Ann. Oncol.* **30**, (2019).

Painter, C. A. *et al.* The Angiosarcoma Project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. *Nature Medicine* **26**, 181–187 (2020).

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* **107**, 639–645 (2012)

Sturm, G. *et al.* Comprehensive evaluation of transcriptome-based cell-type quantification methods for immuno-oncology. in *Bioinformatics* **35**, i436–i445 (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	Candidates must have a first class or upper second class honours BSc Honours/MSc in Biology, Biochemistry, Cancer Biology or a related discipline. SPECIAL REQUIREMENTS • Applicants can be of any nationality • If the applicant's first language is not English: They must be able to demonstrate a proficiency in English to the equivalent of an IELTS score of 7.0, with a minimum of 6 in any one component; -or- within the last two years in a majority English speaking country, have either education experience in English for a minimum of 1 year; or work experience in English for a minimum of 18 months and be able to satisfy Home Office visa criteria where necessary. • Applicants must be eligible to enroll in a PhD programme at the ICR.
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