The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Title:	Integrative computational analysis of molecular and clinical data to dissect heterogeneity of therapy response in sarcomas

SUPERVISORY TEAM	
Primary Supervisor(s):	Dr Paul Huang
Associate Supervisor(s):	Dr Maggie Cheang
Backup Supervisor:	Dr Anguraj Sadanandam
Lead contact person for the project:	Dr Paul Huang

DIVISIONAL AFFILIATION	
Primary Division:	Molecular Pathology
Primary Team:	Molecular and Systems Oncology

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Advanced soft tissue sarcomas (STS) comprise a heterogeneous group of rare mesenchymal cancers where patients suffer from poor outcomes despite treatment with a repertoire of systemic agents. It has been shown that a subset of STS patients benefit from targeted agents including tyrosine kinase inhibitors such as pazopanib and cediranib. However, there are currently no established predictive biomarkers for such therapies in this disease. There is thus a clinical need for the development of novel predictive biomarkers to prospectively select STS patients most likely to benefit from targeted therapy while identifying those patients unlikely to respond to such treatments and who would be better served by alternative treatment.

This studentship will apply machine learning and statistical modelling strategies to identify predictive biomarkers and develop predictive algorithms for targeted therapy treatment based on molecular profiling data generated from multi-centre cohorts of STS patients who have been treated with various therapies including pazopanib, and the CASPS trial - a randomised placebo controlled Phase II trial of cediranib in a form of STS known as alveolar soft part sarcoma (ASPS)

Our goal is to use cutting-edge data-mining techniques in collaboration with experimental and clinical investigators to identify new molecular markers of resistance to treatment in STS. Discoveries from this project will provide the basis for new biomarker-guided clinical trials that will enable personalisation of sarcoma treatment to individual patients whilst providing important new insights into how this class of drugs work in the context of STS.

PROJECT AIMS

- To identify and evaluate ability of the transcriptional and proteomic signatures to predict targeted therapy response using human tissues collected from various studies

- To determine the expression patterns of circulating biomolecules (cytokines and circulating free DNA) over the course of treatment and evaluate the ability of these dynamic changes to monitor response to targeted therapy in STS.
- To identify and validate the clinical validity of molecular subtypes of STS using datasets from publicly available such as The Cancer Genome Atlas.

- To integrate transcriptomic and proteomic with experimental data for identification of candidate genes/proteins and signalling networks associated with intrinsic and acquired targeted therapy resistance; with the goal of working collaboratively with other laboratory-based team members to investigate mechanisms of drug resistance.

RESEARCH PROPOSAL

This proposal seeks to identify predictive biomarkers for response to targeted therapies such as the tyrosine kinase inhibitors (TKIs) cediranib and pazopanib in advanced STS. Cediranib is a multi-target TKI that exhibits selectivity for a spectrum of receptor tyrosine kinases. It has been clinically evaluated for the treatment of alveolar soft part sarcoma (ASPS) in a recent Phase II randomised placebo controlled study of cediranib in ASPS patients (the CASPS trial, NCT01337401, Chief Investigator: Prof Ian Judson). Pazopanib is another multi-target TKI which is the first and currently only TKI approved for most STS subtypes. The Royal Marsden/Institute of Cancer Research have an ongoing translational study which seeks to identify molecular-based biomarkers from pre-treatment specimens in a multi-centre cohort of STS patients who have been treated with targeted therapies. The overarching goal of this studentship is to develop predictive biomarkers for targeted therapies that could be used to guide the personalised management of advanced STS. Working collaboratively with wet lab-based scientists in the team, a secondary focus of the translational project is to perform deep analysis of transcriptomic and proteomic data from these clinical cohorts to identify candidate genes and biological networks that are associated with targeted therapy resistance in patients.

The study will initially focus on work involving integrative analysis of RNA-seq and/or Nanostring-based transcriptomic and mass spectrometry-based proteomic data of clinical specimens from cutting-edge international and multi-centre studies. The goal is to develop de novo and/or validate signatures that can be implemented as predictive biomarkers for drug response. Additionally, the successful candidate will evaluate if dynamic alterations in circulating levels of cytokines and cfDNA at multiple time points during the course of drug treatment have utility in monitoring treatment response in STS patients.

The project is composed of 4 aims.

Aim 1: Identification of transcriptional and proteomic signatures for prediction of targeted therapy response,

Aim 2: Evaluate if changes in the levels of circulating biomolecules (cytokines and circulating free DNA) over the course of treatment are useful in monitoring response to targeted therapy in STS.

Aim 3: Analysis of transcriptomic and proteomic data to identify candidate genes/proteins and signalling networks that are associated with intrinsic and acquired targeted therapy resistance

Aim 4: To identify and validate the clinical validity of molecular subtypes of STS using datasets from publicly available such as The Cancer Genome Atlas.

The student will be trained to apply modern computational approaches, including mathematical and statistical modelling, machine learning and network analysis, to address these aims.

Training and development

The PhD student will be integrated into the multi-disciplinary Molecular and Systems Oncology 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. You will work as part of a team of inter-disciplinary data scientists who are experts in NGS-data analysis, machine learning and software development; and therefore offering unique learning opportunities. There will be a collaboration with the Sarcoma Unit led by Dr. Robin Jones as well as the Chief Investigator of the CASPS trial Prof Ian Judson. This project will be done in close collaboration with Dr Maggie Cheang, an expert in bioinformatics and biostatistics, who leads the Genomics Analysis – Clinical Trials Team within the ICR-Clinical Trials and Statistics Unit. She is co-inventor the breast cancer intrinsic subtypes PAM50 classifier and experienced in integrating clinical data with genomics for association testing. The student will be exposed to STS biology, clinical trials, biomarker discovery and bioinformatics.

LITERATURE REFERENCES

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.

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.

Huang et al., A molecular signature predictive of clinical outcome following pazopanib therapy in advanced soft tissue sarcoma. Annals of Oncology, 28, Issue supp_10, mdx675.001

van der Graaf, W.T., et al., Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet, 2012. **379**(9829): p. 1879-86.

Frezza, A.M., et al., Systemic treatment in advanced soft tissue sarcoma: what is standard, what is new. BMC Med. 15:109.

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 computational subject and have experience in statistical programming and scripting, and must have a basic knowledge of biology
Intended learning outcomes:	• Bioinformatics – integrated analysis of high-throughput data (Next Generation Sequencing, targeted transcriptomic and proteomic) • Biostatistics – Bayesian and machine learning methods to develop biomarker response classifiers. • Programming in R, STATA (or SPSS) and in any one high-level programming language (C/C++, Perl or Python) • Basic knowledge of *NIX systems and shell scripting • Knowledge in sarcoma biology and cancer therapeutics • 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. Biomarkers
	3. Molecular Profiling or statistical genomics
	4. Computer science / artificial intelligence
	5. Machine learning, statistical modelling
	6. Kinase inhibitors