The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Title:	Deconstructing the sarcoma matrisome for drug target and biomarker discovery

SUPERVISORY TEAM	
Primary Supervisor:	Paul Huang
Additional members of the supervisory team:	Robin Jones
Lead contact person for the project:	Paul Huang

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

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Resistance to chemotherapy and targeted therapy remains the leading cause of death in patients with advanced soft tissue sarcoma (STS). While large-scale molecular analysis of the genomics and epigenetics of STS tumours has deepened our understanding of the pathology of the disease, there remains a large gap in translating this knowledge into better treatments for sarcoma patients. In contrast to the tumour cell compartment, the biology of the tumour microenvironment (TME) in STS, specifically the TME component comprising the extracellular matrix and associated proteins (collectively known as the matrisome), remains largely unknown. Notably, the matrisome has been shown in other cancer types to be a rich source of therapeutic targets and prognostic biomarkers. The objective of this proposal is to harness the power of proteomics to characterise, in unprecedented detail, the sarcoma matrisome across multiple histological subtypes and between matched primary and relapsed specimens. By defining the dynamic matrisomal remodelling associated with tumour relapse and drug resistance, our novel approach will identify new prognostic biomarkers for survival and candidate drivers of chemoresistance in STS. Leveraging on patient-derived hydrogels and decellularised scaffolds for preclinical validation of these candidate targets, we anticipate that this research will lead to the discovery of innovative salvage therapies to achieve the goal of durable drug responses and ultimately improved sarcoma patient outcomes.

PROJECT AIMS

1. **Define the matrisome alterations associated with poor response to chemotherapy by profiling clinical cohorts of STS specimens**
2. **Identify prognostic matrisome signatures and candidate drivers of chemoresistance**
3. **Experimental assessment of candidate chemoresistance drivers in preclinical models**

RESEARCH PROPOSAL

In contrast to the deep molecular analysis that has been undertaken in the tumour cell compartment, the stroma component of STS remains poorly studied. In particular, the composition of the extracellular matrix (ECM), ECM-associated proteins and secreted proteins (collectively known as the matrisome) in the stroma is largely unknown. In epithelial cancers such as breast and lung cancer, multiple studies have shown that these matrisomal components are drivers of drug resistance. **Our hypothesis is that the matrisome undergoes dynamic remodelling in response to therapy, which ultimately drive drug resistance and tumour relapse in STS.** To test this hypothesis, we will employ proteomics and transcriptomics to perform deep characterisation of matrisomal alterations across major histological subtypes and matched primary and recurrent disease; assess the potential of matrisomal signatures for prognostication in STS outcomes, and experimentally test candidate matrisomal drivers of drug resistance in patient-derived hydrogels and decellularised scaffolds. By providing the first-ever molecular portrait detailing the evolution of the STS matrisome in response to therapy, this translational research project will address an existing knowledge gap in our understanding of sarcoma biology and clinical course of the disease. We anticipate that this study will have a direct impact on improving patient outcomes by delivering new strategies to combat drug resistance and identify robust prognostic biomarkers.

The project is composed of 3 aims.

Aim 1: Undertake matrisome profiling by proteomics and transcriptomics from archival FFPE tumour specimens in a cohort of STS specimens across 3 major histological subtypes.

Aim 2: Our underlying hypothesis is that matrisomal components that are associated with poor outcome or enriched in relapsed versus primary specimens are potential drivers of chemoresistance. To identify these matrisomal components which are candidate chemoresistance drivers, profiling data from Aim 1 will be linked to anonymised clinical data.

Aim 3: Candidate matrisomal components will be assessed in a panel of sarcoma cell lines to evaluate their ability to induce resistance to a panel of approved STS drugs. Additionally, 3D spheroid cultures using patient drived hydrogels and decellularised scaffolds will also be used to assess matrisomal drivers of resistance.

This project will bridge our understanding of the dynamic matrisomal alterations associated with poor response to chemotherapy and distil key TME dependencies in STS patients. The proposed study will accelerate the identification of an entirely new class of salvage therapies to combat drug resistance as well as novel prognostic biomarkers. In the longer term, working together with The Royal Marsden Sarcoma Unit, we anticipate that such treatments could be evaluated in trials for their efficacy in delivering better outcomes in patients.

Training and development

The PhD student will be integrated into the multi-disciplinary Protein Networks Team in the Division of Molecular Pathology and the Joint Royal Marsden-ICR Sarcoma Research Centre. 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. The student will gain hands-on experience in molecular profiling strategies, cell and molecular biology and

molecular pathology. The student will be exposed to Cancer Biology, Proteomics, Tumour Microenvironment, and Sarcoma Molecular Pathology.

LITERATURE REFERENCES

1. Krasny, L., et al., SWATH mass spectrometry as a tool for quantitative profiling of the matrisome. J Proteomics, 2018.
2. Krasny, L., et al., Comparative proteomic assessment of matrisome enrichment methodologies. Biochem J, 2016. **473**(21): p. 3979-3995.
3. Linch, M., et al., Systemic treatment of soft-tissue sarcoma-gold standard and novel therapies. Nat Rev Clin Oncol, 2014. **11**(4): p. 187-202.
4. Cancer Genome Atlas Research Network. Comprehensive and Integrated Genomic Characterization of Adult Soft Tissue Sarcomas. Cell, 2017. **171**(4): p. 950-965 e28.
5. Gaebler, M., et al., Three-Dimensional Patient-Derived In Vitro Sarcoma Models: Promising Tools for Improving Clinical Tumor Management. Front Oncol, 2017. **7**: p. 203.
6. Hynes, R.O. and A. Naba, Overview of the matrisome--an inventory of extracellular matrix constituents and functions. Cold Spring Harb Perspect Biol, 2012. **4**(1): p. a004903.
7. Pouliot, R.A., et al., Development and characterization of a naturally derived lung extracellular matrix hydrogel. J Biomed Mater Res A, 2016. **104**(8): p. 1922-35.
8. Pearce, O.M.T., et al., Deconstruction of a Metastatic Tumor Microenvironment Reveals a Common Matrix Response in Human Cancers. Cancer Discov, 2018. **8**(3): p. 304-319.

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, molecular pathology, 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.