The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL

PROJECT DETAILS	
Project Title	Deep multi-omic integration to understand inter-organ relationships that regulate systemic immunometabolism
Short Project Title	Deep multi-omic integration to understand systemic immunometabolism

SUPERVISORY TEAM	
Primary Supervisor	Yinyin Yuan
Associate Supervisor(s)	Stephanie Ling
Secondary Supervisor	Pascal Meier

DIVISIONAL AFFILIATION	
Primary Division	Molecular Pathology
Primary Team	Computational Pathology
Site	Sutton

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

One of the fundamental questions in biology is how systemic metabolism affects immune response. In normal human biology, multiple organs act in concert to maintain metabolic homeostasis and protect against the onset of disease.

The functions of immune cells are in turn closely modulated by their metabolic environment, and the metabolism of many immune cells is altered upon their activation. Improved understanding of the interplay that exists between the host immune response and key metabolic tissue, such as the liver, heart and kidney, will provide critical insights into the mechanisms that govern 'metabolic-immune' crosstalk and the biological systems in place to defend against metabolic disease. For example, early activation of key immune cell subtypes by metabolic factors that exist within their microenvironment environment may provide early-warning signals that precipitate a host response to perceived metabolic stress.

Establishing a systematic model of the role of metabolic regulation and its cross-talk with the immune system will enable greater understanding of the physiological systems in place to defend and against metabolic stress. The complexity this interaction in immunometabolism, and the interplay between different tissues mean that an integrated approach is required to fully understand how systemic metabolism and the immune system interact.

At AZ, our cutting-edge capabilities enable routine systematic interrogation of tissue biology using spatial resolved transcriptomics, proteomics and metabolomics. However, the scale and complexity of these data mean we are currently limited to testing specific hypotheses and are yet to implement systematic data-driven approaches that use the information available to its full potential.

This gap will be bridged by using deep multi-omic integration methodologies developed at the Yuan Lab at ICR, linking histological signatures, gene expression profiles, cell signalling and metabolic states. For the first time, we will generate a model describing the mechanism and relative contribution and interplay between key organs in response to early metabolic dysregulation and inflammation.

PROJECT AIMS

Aims:

1) Build from existing multimodal integration work of spatially resolved imaging techniques to define multicellular molecular and morphological signatures of tissue associated with metabolic dysregulation in the liver, kidney, and heart and the associated resident and infiltrating immune microenvironment phenotypes.

2) Interpretation of transcriptomic data in models of metabolic syndrome have been confounded by inability to distinguish transcriptomic shift from cellular remodelling. Use multicellular signatures from IMC for better understanding of the cell types contributing to the transcriptomic changes associated with early changes in metabolism detected in each organ. Deep learning integration will then be used to distinguish data resulting from differential cell infiltration and regulated gene expression.

3) Matched clinical data for better understanding of systemic immunometabolism and model translation with the potential for novel target identification.

4) Build a spatiotemporal model of multicellular signalling, inflammation and metabolomic interdependencies to produce a dynamic model of the aetiology and contribution of each organ during normal systemic function and upon perturbation such as in early and established metabolic dysfunction.

RESEARCH PROPOSAL

There a growing core and breadth of expertise in data science and AI at AstraZeneca, with functions focussed on working towards integration of one or multi-omic datasets, and ongoing efforts to coregister and integrate multiple different imaging modalities. Whilst we are realising these types of integration, we have not yet attempted to integrate bulk-omic data with spatially resolved omic data and traditional pathology. This project therefore represents an opportunity where the diverse expertise represented at AstraZeneca in generating and handling these data types will be complimented by the external collaborator's specific expertise to combine digital pathology with large-scale omics to mine key information associated with spatially resolved phenotypes in biological tissues.

Dr Yuan's lab at ICR have developed sophisticated AI based 'image-omics' techniques to integrate digital pathology and omics data. Deploying spatial statistics widely used in ecology, they infer tissue spatial heterogeneity and niche characteristics within a complex cellular network and demonstrated that the immune ecological environment co-evolves with genetic diversity within patients to drive immune evasion.

We propose an innovative approach transferring learning among heterogeneous multi-omic datasets in derived from pre-clinical models and well-characterised clinical samples. Multi-omic integration of histology and detailed spatial architectural information with complex cellular diversity has not yet been attempted. Using deep learning analysis of diverse phenotypic and geospatial features, we will advance this approach to incorporate the unique spatially resolved omic data generated at AZ with the detailed breakdown of cellular composition and single cell signalling made possible by high-plex Imaging Mass Cytometry (IMC) to resolve, and to mine tissue region-level omic data.

Whilst we can co-register and fuse multiple data types with matched spatial features, combining spatially resolved imaging-based data with bulk-level omics data remains challenging. The breadth of high-plex imaging and omics datasets generated in-house, combined with the Yuan lab's expertise in multi-omic integration present a unique and unexplored opportunity to develop novel data analysis approaches to gain deeper insights into the complex biological processes that govern multi-organ cross-talk with unprecedented detail.

In this project, by combining this expertise with that at AstraZeneca and the existing breadth of multimodal, multi-omic data we have generated, we hope to drive these capabilities further and enable new insights into the interplay between metabolism and the immune response. The new methodologies developed in this project would have broad-reaching implications, including the role of inflammation in metabolic diseases such as diabetes, NASH and cardiovascular disease, the role of microenvironmental metabolism in autoimmunity and in the tumour microenvironment in immune-oncology.

As this project will be principally data science based, the student will be able to work at either AstraZeneca or ICR, or indeed remotely if needed. There shall be weekly catch ups with the student, with collaboration tools such as Microsoft teams enabling ongoing offline interactions.

The stated aim of this project shall be to publish both the methodology developed by the student, and to publish any insights into systemic immunometabolism that they might find. We will use existing data from mouse models and clinical biopsies, but will aim to exclude data from drug treatments, and so do not anticipate that there will be any IP issues. This

project is focused on understanding systems-level biology and is not linked to a specific disease target. We also have documented agreement for the technologies used to generate the data to enable timely publications.

The insights gained in this project will provide innovative insights into this multi-organ interplay and may identify the factors that drive an aberrant host response to help drive new preventative strategies that mitigate against inflammatory and metabolic disease, such as through modulation of local environmental and lifestyle factors or through identification of novel targets amenable therapeutic manipulation.

LITERATURE REFERENCES

1. AbdulJabbar K^, Raza SEA^, Rosenthal R†, Jamal-Hanjani M†, Veeriah S†, Akarca A, Lund T, Moore D, Salgado R, Bakir MA, Zapata L, Hiley CT, Officer L, Sereno M, Smith CR, Loi S, Hackshaw A, Marafioti T, Quezada SA, McGranahan N, Le Quesne J*, Swanton C*, **Yuan Y*** (2020). Geospatial immune variability illuminates differential evolution of lung adenocarcinoma, Nature Medicine, 26, 1054–1062.

2. Failmezger H^, Muralidhar S^, Rullan A, de Andrea CE, Sahai E, **Yuan Y*** (2020). Topological Tumor Graphs: a graph-based spatial model to infer stromal recruitment for immunosuppression in melanoma histology, Cancer Research, IF:9, DOI: 10.1158/0008-5472.CAN-19-2268.

3. Heindl A, Khan AM, Rodrigues DN, Eason K, Sadanandam A, Orbegoso C, Punta M, Sottoriva A, Lise S, Banerjee S, **Yuan Y*** (2018). Microenvironmental niche divergence shapes BRCA1-dysregulated ovarian cancer morphological plasticity, Nature Communications, IF:12, 9:3917.

4. Heindl A, Sestak I, Naidoo R, Cuzick J, Dowsett M, **Yuan Y*** (2018). Relevance of spatial heterogeneity of immune infiltration for predicting risk of recurrence after endocrine therapy of ER+ breast cancer, JNCI: Journal of the National Cancer Institute, IF:12, 110(2), djx137.

5. Natrajan R, Sailem H, Mardakheh FM, Arias MG, Dowsett M, Bakal C, **Yuan Y*** (2016). Microenvironmental heterogeneity parallels breast cancer progression: A histology-genomics integration analysis, PLoS Medicine, IF:11, 16;13(2):e1001961.

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7. Raza SEA, AbdulJabbar K, Jamal-Hanjani M, Veeriah S, Le Quesne J, Swanton C, **Yuan Y*** (2019), Deconvolving convolution neural network for cell detection, IEEE International Symposium on Biomedical Imaging (ISBI) 2019.

8. Narayanan PL*, Dodson A, Gusterson B, Dowsett M, and **Yuan Y*** (2018), DeepSDCS: Dissecting cancer proliferation heterogeneity in Ki67 digital whole slide images, Medical Imaging in Deep Learning (MIDL 2018).

9. Zormpas-Petridis K, Failmezger H, Raza SEA, Roxanis I, Jamin Y, **Yuan Y*** (2019). Superpixel-based Conditional Random Fields (SuperCRF): Incorporating global and local context for enhanced deep learning in melanoma histopathology. Frontiers in Oncology, 9: 1045, doi.org/10.3389/fonc.2019.01045.

10. Zormpas-Petridis K*, Failmezger H, Roxanis I, Blackledge MD, Jamin Y, **Yuan Y*** (2018). Capturing global spatial context for accurate cell classification in skin cancer histology, Medical Image Computing and Computer Assisted Intervention (MICCAI) COMPAY workshop 2018.

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)	
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.	
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)