

The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS

Project Title:	Deep learning to guide immunology for the discovery of immune-oncology targets
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Primary Supervisor:	Yinyin Yuan
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Backup Supervisor:	Alan Melcher
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Lead contact person for the project:	Yinyin Yuan
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DIVISIONAL AFFILIATION

Primary Division:	Molecular pathology
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Primary Team:	Computational pathology
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PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Systemic immunotherapy has revolutionised the therapeutic landscape of cancer. However, the fact remains that the majority of patients do not respond to treatment. This is because the rapid advances in clinical cancer immunotherapy have not been matched by a detailed understanding of diverse immune response and resistance occurring in human tumours. Towards this, a major obstacle is our lack of understanding in cancer as an evolutionary and ecological process. Cancer cells have the ability to remodel and adapt to selective pressure from the immune system according to Darwinian theory, underscoring the need for systematic efforts to elucidate the rules governing interplay between cancer and immune cells.

However, to date we are limited by current approaches to study the relationship among immune response, cancer molecular alterations and clinical phenotypes. It is becoming increasingly evident that we need to develop advanced, spatially explicit computational and experimental approaches to study complex cancer-immune interactions. We believe that the development of a new type of methodology that combines diagnostic pathology with experimental immunology, enabling spatial mapping of intra-tumour heterogeneity and microenvironmental characteristics, will change the way we study cancer and enhance our ability to deliver precision medicine.

This project will build a multidisciplinary collaboration bridging artificial intelligence, multiplex immunolabelling and tumour immunology between the three lead supervisors with complementary expertise and track record:

Lead supervisor:

Dr Yinyin Yuan, Computational Pathology and Integrated Genomics, The Institute of Cancer Research, London, UK

Associated supervisors:

Prof Teresa Marafioti, Department of Cellular Pathology, University College London, London, UK

Prof Sergio Quezada, Cancer Immunology Unit, University College London Cancer Institute, London, UK

Hypothesis

Our hypothesis is that alterations in the cancer genome are directly implicated in immune regulation, as a result of adaptation and selection by the immune system. The ability of deep learning in discerning visual patterns and learn critical structure in high-dimensional datasets thus provides an excellent opportunity to identify new and targetable genes essential for immune regulation.

PROJECT AIMS

Using AI, digital pathology and immunology, the student will:

1. Develop a deep learning and computer vision software suite for a pan-cancer analysis across 9,404 tumours and 19 cancer types at single-cell resolution to quantitatively define diverse spatial patterns of immune response;
2. Develop a deep learning algorithm to integrate genomic alterations enriched in tumours with the immune response phenotypes and identify potential immune modulators;
3. Use multiplex immunohistochemistry and immunofluorescence in focus cancer types to test putative genes identified and associated changes in the immune microenvironment.

RESEARCH PROPOSAL

Deep learning at the forefront of artificial intelligence (AI) has emerged as the new frontier in computer vision and big data analysis. It therefore holds great promise to transform pathology following digitalisation. As now widely recognised, digital pathological could be central to modern molecular pathology, biomarker discovery, and precision medicine. We have pioneered statistical approaches to harness rich spatial data from digital pathology to study tumours as ecosystems. Herein, we propose to train a next-generation PhD researcher in artificial intelligence, digital pathology, and immunology, thereby delivering deep learning and digital pathology innovations for the discovery of novel immune regulatory and suppressive pathways.

This project will focus on three cancer types with urgent unmet needs, with the discovery analysis at a pan-cancer scale to determine the potential spread of impact of identified targets. We will demonstrate that such fully integrative approaches will deliver novel immune phenotypes as potential biomarkers, directly enabling the identification of targetable immune regulatory pathways. The ability to directly couple new drugs with biomarkers will fundamentally change the way we deliver cancer therapies with maximum therapeutic efficacy and minimal drug resistance.

Through the training of a PhD researcher in artificial intelligence, digital pathology, and immunology, this project will define diverse immune response in tumours, to help develop and evaluate novel therapeutic strategies guided by digital biomarkers, and to accelerate the delivery of digital pathology into the day-to-day clinic. Deliverables of this project will include new software and methodology developments in deep learning pipelines for automated and generalisable histology image analysis, integration of image-omics, and multiplex image analysis, and new scientific data for:

- 1) a rich histology dataset across 20,000 samples that deconvolutes the microenvironments into spatially explicit architectural patterns at single-cell resolution; Similarity and difference in the clinical relevance across cancer types;

- 2) a catalogue of spatial interactions among diverse cell types, inferred from multiplex staining to corroborate bioinformatics inference;
- 3) inferred functional roles of new, putative immune modulators

LITERATURE REFERENCES

1. Vargas, F. A. *et al. Cancer Cell* **33**, 649–663.e4 (2018).
2. Heindl, A. *et al. J. Natl. Cancer Inst.* **110**, (2017).
3. Turajlic, S. *et al. Lancet Oncol.* **18**, 1009–1021 (2017).
4. Saltz, J. *et al. Cell Rep.* **23**, 181–193.e7 (2018).
5. Heindl, A. *et al. Nat. Commun.* **9**, 3917 (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)

BSc or MSc in computer science, bioinformatics, or equivalent quantitative disciplines

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.

- expertise in the development of deep learning algorithms,
- expertise in the development of digital pathology software,
- transferable skills and competency in programming and image processing,
- experience in experimental approaches including multiplex immunohistochemistry
- experience working in a highly translational and collaborative research environment.