ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	Christine O'Connell of *One More City*

Project details

Project title:	Multimodal dissection of metastatic breast cancer at the single cell resolution

Supervisory team

Primary Supervisor:	Professor Victoria Sanz-Moreno
Associate Supervisor(s):	Dr Syed Haider
Secondary Supervisor:	Dr Rachael Natrajan

Divisional affiliation

Primary Division:	Breast Cancer
Primary Team:	Cytoskeleton and Metastasis Team
Site:	Chelsea

Project background

Nearly all deaths related to breast cancer are in patients with metastatic, secondary, disease. Understanding how metastatic niches support breast cancers and how metastatic disease might be targeted is critical. We have made a significant contribution in the understanding of how Rho-ROCK-Myosin II driven cytoskeletal remodelling plays a key role in defining metastatic behaviour. Abnormal cell migration is a characteristic of cancer cells. Epithelial cells become motile by undergoing epithelial-to-mesenchymal transition (EMT) which involves downregulation of E-cadherin expression, a characteristic of many breast cancers. Mesenchymal cells increase migration speed by increasing Rho-ROCK-Myosin II and adopting amoeboid or bleb-based migration strategies using mesenchymal to amoeboid transition (MAT). In some cases, we have identified direct epithelial to amoeboid transition (EAT). Importantly, amoeboid cancer cells are enriched at the borders of tumours and in metastasis.

Our recent work highlights that Rho-ROCK-Myosin II driven cytoskeletal dynamics and "amoeboid behaviour" is characterised by a pro-invasive, pro-survival and immunosuppressive transcriptional program that allows these cells to colonise challenging metastatic microenvironments. As such, characterising amoeboid tumour cell behaviour and associated cytoskeletal dynamics is crucial if we are to treat secondary breast cancer.

On the other hand, tumours are heterogeneous so that it is important to understand if all amoeboid or all invasive cancer cells are the same or there are different "amoeboid states" or different "invasive and metastatic states". To understand this, we will use in vivo spatial-temporal single cell approaches to profile metastatic tumours and their tumour micro-environment (TME) at single cell resolution. The resulting large-scale data will be integrated and interpreted using in-silico statistical modelling and data mining techniques.

In this project, we will investigate if breast cancer cells found at the border of primary tumours resemble those found in metastatic lesions and/or significant changes take place.

Project aims

- Characterise invasive cancer cells and their TME at the border of triple negative breast cancer primary tumours- at single cell resolution
- Characterise metastatic cells and TME at single cell resolution
- Identify key transcriptional/epigenetic regulators of the different invasive and metastatic states
- In collaboration with wet lab biologists, design functional assays to block invasion and metastasis via targeting of key transcriptional/epigenetic regulators.

Research proposal

In this project, the student will have access to multi modal data: bulk RNA sequencing, proteomics and phospho-proteomics, single cell RNA sequencing, ATAC sequencing, spatial metabolomics, and spatial transcriptomics data.

We will focus on commonalities between cell populations (cancer and non-cancer) present in the invasive areas of the primary tumour and in the metastatic lesions.

The project will investigate if there are different and/or conserved invasive and/or metastatic breast cancer transcriptional states linked to cytoskeletal features in different parts of the primary tumour and compare with different areas at the metastatic site. We will analyse these features over time to understand if these states are stable or if they change with disease progression.

As the project aims to generate high-throughput multimodal sequencing datasets at a single cell resolution, the student will be required to learn and develop (where necessary), state-of-the-art computational data mining algorithms for the identification of transcriptional signatures of local invasion and metastasis, as well as data-integration approaches suitable for these data. Finally, integration and validation of identified signatures in publicly available genomic and clinical datasets will be performed by the student.

In collaboration with the wet lab biologists, cancer cells from different areas will be studied for functional activity linked to their transcriptional state.

For functional studies, we have developed systems to study the cytoskeleton coupled to transcriptional activity. Collagen I- 3D models will be used to measure invasive growth. Mouse models will be used to measure metastatic potential.

We aim to manipulate the key transcriptional programs found to drive local invasion and secondary tumour growth. We will combine our observations with triple negative breast cancer patient data analysis using spatial digital pathology to confirm that some of the key players found in OMICs studies are biomarkers of metastatic behaviour.

The goal is to define all the possible invasive and metastatic states (and find some unique common features to all of them) and to target the pro-metastatic “transcriptional addiction” linked to cytoskeletal dynamics.

Literature references

[1] Graziani, V., et al., The amoeboid state as part of the epithelial-to-mesenchymal transition programme. Trends in Cell Biology, 2022. 32(3): p. 228-242.
[2] Crosas-Molist, E., et al., Rho GTPase signaling in cancer progression and dissemination. Physiological Reviews, 2021. 102(1): p. 455-510.
[3] Maiques, O., et al., A preclinical pipeline to evaluate migrastatics as therapeutic agents in metastatic melanoma. British Journal of Cancer, 2021. 125(5): p. 699-713.
[4] Rodriguez-Hernandez, I., et al., WNT11-FZD7-DAAM1 signalling supports tumour initiating abilities and melanoma amoeboid invasion. Nature Communications, 2020. 11(1): p. 5315.
[5] Georgouli, M., et al., Regional Activation of Myosin II in Cancer Cells Drives Tumor Progression via a Secretory Cross-Talk with the Immune Microenvironment. Cell, 2019. 176(4): p. 757-774.e23.

[6] Orgaz, J.L., et al., Myosin II Reactivation and Cytoskeletal Remodeling as a Hallmark and a Vulnerability in Melanoma Therapy Resistance. Cancer Cell, 2020. 37(1): p. 85-103.e9.
[7] Perdrix Rosell, A., et al., Early functional mismatch between breast cancer cells and their tumour microenvironment
[8] Samain, R., et al., CD73 controls Myosin II–driven invasion, metastasis, and immunosuppression in amoeboid pancreatic cancer cells. Science Advances. 9(42): p. eadi0244.
[9] Crosas-Molist, E., et al., AMPK is a mechano-metabolic sensor linking cell adhesion and mitochondrial dynamics to Myosin-dependent cell migration. Nature Communications, 2023. 14(1): p. 2740.
[10] Jung-Garcia, Y., et al., LAP1 supports nuclear adaptability during constrained melanoma cell migration and invasion. Nature Cell Biology, 2023. 25(1): p. 108-119.

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:	Quantitative background (Computer science or Biostatistics or Engineering or Mathematics) OR Biology/biomedical related discipline with demonstrable education and experience in a quantitative discipline.
Intended learning outcomes:	• Data mining and data integration of multimodal single cell datasets • Understanding cytoskeletal dynamics • Understanding metastasis biology • Understanding transcriptional control of cellular states

Advertising details

Project suitable for a student with a background in:

- ☒ Biological Sciences
- ☒ Physics or Engineering
- ☐ Chemistry
- ☒ Maths, Statistics or Epidemiology
- ☒ Computer Science