ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by: EU

Project details

Project title:

Triple Negative Breast cancer control of the immune tumour microenvironment in metastasis

Supervisory team

Primary Supervisor: Prof Victoria Sanz Moreno

Associate Supervisor(s):

Secondary Supervisor: Prof Andrew Tutt

Divisional affiliation

Primary Division: Breast Cancer Research

Primary Team:

Cytoskeleton and Cancer Metastasis Team

Site: Chelsea

Project background

Metastasis, the spread of cancer to secondary organs, accounts for approximately 90% of cancer-related deaths mainly due to resistance to conventional treatments and organ failure. Unfortunately, our understanding of metastasis evolution, from its onset to treatment resistance, remains limited. Although natural selection acts on phenotypes, cancer research has traditionally focused on genotype alterations. Despite extensive efforts, specific genetic alterations that would confer metastatic functions have not yet been identified. In addition, the regulation of a cell´s phenotypic output is multi-layered, with both transcriptional and epigenetic mechanisms playing key roles. To address these crucial gaps in knowledge, we have established the ADAPTMET consortium.

The goal of the consortium is to bolster basic research on metastatic cancers, ultimately influencing drug development and improving the clinical standard of care. This initiative aligns with the solution-oriented missions of Horizon Europe, with cancer being one of its priority areas.

Cancer progression involves two central capabilities: invading the stroma and adapting to hostile environments when colonising secondary organs. The vasculature plays a crucial role in tumour progression and therapy response, sharing signalling and metabolic pathways with cancer cells. Other stromal cells such as fibroblasts exhibit similar

behaviour whereas the immune cell repertoire may support or limit progression owing to a complex integration of systemic and local cues. Our approach combines state-of-the-art experimental systems with clinical analyses to dissect the mechanisms of tumour-stroma interaction in metastasis.

Extensive experimental evidence suggests that the tumour microenvironment and metastatic niches are potential targets for therapy. To this end, endothelial, fibroblast and immune cell driven engineered mouse models within this consortium represent unique opportunities.

In our group based at ICR, we have previously found that TNBC primary tumours in which we block Myosin driven cytoskeletal dynamics generate a less supportive TME (specifically fibroblasts and macrophages significantly change).

We will explore if similar mechanisms are operative during metastatic organ colonisation and outgrowth in the lung and in the brain- which are two key metastatic sites for TNBC.

We aim to find key vulnerabilities of metastatic TNBC cells that could be clinically targeted.

Project aims

- This project will focus on:
- Characterisation on how Myosin driven cytoskeletal dynamics blockade generates a less supportive TME in metastasis.
- Studying how these adaptive mechanisms operate during metastatic organ colonisation (early lung colonisation and micro-metastasis stages) and outgrowth (macro-metastasis development)
- Using gained knowledge to identify therapeutic vulnerabilities of amoeboid metastatic TNBC cells that could be clinically targeted.
- We will use patient tissue material to identify micro-niches (in the lung and the brain) that are supportive of metastatic outgrowth and that are relevant in the human setting.
- Planned secondment(s): to understand how cancer cell cytoskeletal dynamics may alter microglia and brain macrophages, the student will spend a period at Prof Johanna Joyce's lab at the University of Lausanne.

Research proposal

Aim and overview

Metastasis is the principal cause of death in many cancers and is in part driven by a subset of aggressive cells adopting an amoeboid cellular state, enabling them to survive, migrate away from primary tumours and colonise challenging microenvironments while escaping current therapeutic approaches.

Abnormal cell migration is characteristic of disseminating cancer cells and is driven by cytoskeletal remodelling. Epithelial cells become motile by undergoing epithelial-to-mesenchymal transition (EMT), while mesenchymal cells increase migration speed by adopting amoeboid features. We have described how amoeboid behaviour is not merely a migration mode but a cellular state - within the EMT continuum - by which cancer cells survive, invade and colonise challenging microenvironments.

We found an enrichment in amoeboid cells at the border of primary tumours and at the border of metastatic lesions in several tumour types. The tumour edge represents a unique structure in which cancer cells are more exposed to matrix, stromal cells and immune infiltrate. Invading and disseminating cells must overcome immune cell attack in their way to a secondary site, so they develop immunosuppressive strategies.

In this project we will focus on studying the interactions that amoeboid cancer cells establish with the metastatic niche, with a particular focus on TNBC metastasizing to lung and brain and the specific interactions with immune cells in those organs.

For this purpose, 3D co-culture systems and organoids, mouse models and patient samples will be used to dissect the specific crosstalk between amoeboid cancer cells and the TME supporting their metastatic abilities.

The specific objectives of this PhD will be:

i) Characterisation on how Myosin driven cytoskeletal dynamics blockade generates a less supportive TME in metastasis.

For this purpose, we will study the secretome of highly metastatic TNBC cells and we will manipulate using ROCK-Myosin II inhibitors (we will use cytokine arrays and mass spectrometry to analyse proteins and metabolites). Both classical secretion and EV secretion will be compared, and top candidate secreted factors (proteins or metabolites) will be interrogated for the possible effects on monocyte/macrophage fate and function.

ii) Studying how these adaptive mechanisms operate during metastatic organ colonisation

We will compare early lung colonisation and micro-metastasis stages with metastatic outgrowth or macro-metastasis development. We have generated single cell data (VSM lab unpublished) on the TME of murine TNBC in the early and late stages of lung colonisation and outgrowth. We will generate a similar dataset after brain colonisation/outgrowth and will compare how innate immune responses are conserved/different after manipulation of the Myosin II cytoskeleton in cancer cells. We will study the brain TME in more detail since this is a very challenging microenvironment but also TNBC that has metastasized to the brain is very difficult to treat. The student will also have a secondment at the University of Lausanne under the guidance of Prof Johanna Joyce who is an integral member of ADAPTMET. Since we have a special interest in tumour associated macrophages, we will exploit Prof Joyce's expertise in the brain TME to understand how cytoskeletal dynamics may alter microglia and brain macrophages.

iii) Using gained knowledge from all above objectives, we will identify therapeutic vulnerabilities

We will study vulnerabilities of amoeboid metastatic TNBC cells and the myeloid populations they recruit and/or corrupt- that could be clinically targeted. Using mouse models, we will validate how depletion of the most promising protein/metabolite candidates secreted by metastatic cancer cells (and regulated by ROCK-Myosin II) affect metastatic success and innate immune responses.

iv) We will use patient tissue material provided by Prof Andrew Tutt to identify pro-metastatic micro-niches

We will compare tissue sections from the primary tumour (invasive vs non-invasive areas) and sections from lung and brain metastasis. We will validate specific cancer cell-macrophage interactions with appropriate immunohistochemical approaches.

The overarching aim of this PhD is to study how metastatic breast cancer cells communicate with myeloid cells that support their survival and growth in secondary organs such as the brain and the lung. The knowledge we will gain will be used to design future anti-metastasis approaches.

Literature references

[1] Samain R, Maiques O, Monger J, Lam H, Candido J, George S, Ferrari N, KohIhammer L, Lunetto S, Vilardell F, Olsina JJ, Matias-Guiu X, Sarker D, Biddle A, Balkwill FR, Eyles J, Wilkinson RW, Kocher HM, Calvo F, Wells CM, Sanz-Moreno V (2023) CD73 controls Myosin II driven invasion, metastasis and immunosuppression in amoeboid pancreatic cancer cells. Science Advances https://doi.org/10.1126/sciadv.adi0244

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[4] Jung-Garcia Y, Maiques O, Monger J, Rodriguez-Hernandez I, Fanshawe B, Domart MC, Renshaw M, Marti RS, Matias-Guiu X, Collinson LM, Sanz-Moreno V* & Carlton JG* (2023) *co-corresponding co-senior authors. LAP1 regulates nuclear plasticity to enable melanoma constrained migration and invasion. Nature Cell Biology https://doi.org/10.1038/s41556-022-01042-3

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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:	At least a 2:1 degree in a relevant scientific subject Some experience of cell biology and animal experimentation is preferred but exceptional candidates in other disciplines will be considered
Intended learning outcomes:	• Cell biology: tissue culture, 3D biology and microscopy techniques • Mouse in vivo work • Tissue pathology collection and analysis • Computational and quantitative skills: Use of in silico tools for data analysis • Communication: Ability to present work verbally and in writing to a multidisciplinary audience, including writing and submitting of papers to high impact peer-reviewed journals Teamwork: experience of working in a multidisciplinary research team

Advertising details

Project suitable for a student with a background in:

- [x] Biological Sciences
- [ ] Physics or Engineering
- [ ] Chemistry
- [ ] Maths, Statistics or Epidemiology
- [ ] Computer Science