An explant-in-chip platform to study immune-cancer cell interactions and enhance tumour immunogenicity *ex vivo*: A focus on radiotherapy

Supervisors:

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Research Summary

Aims:

1. To develop a platform to investigate immune-cancer cell interactions and their spatiotemporal dynamics within perfused murine tumour explants ex vivo.
2. To optimise radiotherapy parameters (dose, fractionation) to initiate an anti-tumour immune response.
3. To determine the role of tumour-associated fibroblasts on immune suppression.

Hypothesis: Radiotherapy can enhance tumour immunogenicity and promote T-cell recruitment to potentially overcome immunosuppressive effects of tumour associated fibroblasts, but spatiotemporal dynamics play a key role in this process.

Rationale: Although immune checkpoint inhibitors (ICPIs) have achieved great success in melanoma and a number of tumour types, ICPIs only benefit around 12% of patients across the breadth of cancer. One reason is likely because many tumours are immunologically “cold”, containing few cytotoxic CD8+ and conventional/effector CD4+ T-cells, dendritic cells and M1-polarised macrophages and high numbers of immunosuppressive Tregs, tumour associated fibroblasts and M2-polarised macrophages.

A promising approach to improve ICPIs is to combine them in combination with therapies which stimulate a de novo immune response, using additional agents such as oncolytic viruses, immune adjuvants, chemotherapy or radiotherapy. The aim is to cause local cell damage and release of damage-associated molecular patterns (DAMPs) to recruit effector T-cells and antigen-presenting dendritic cells, causing an immune “cold” tumour to become “hot”. Multiple clinical trials are underway to investigate these approaches in combination with ICPIs but results to date have been mixed. What is lacking is a means to directly investigate and optimise how immune stimulants drive (or conversely inhibit) the immune response. As the immune response depends critically on the tumour microenvironment (TME), most research has focussed on in vivo models. But, as with all in vivo work, this limits the parameter space that can be explored for optimisation, and precludes access to the spatiotemporal dynamics of immune-cancer cell interactions, which are of prime importance for ICPI success.

To overcome challenges facing in vivo studies, some have turned to organ-on-chip (OoC). A concern, however, is whether conventional “bottom-up” OoC models, which are highly idealised, adequately capture the TME to sufficiently replicate the immune response. Recognising this limitation, the Overby laboratory developed a “top-down” explant-in-chip model that captures the native TME, in its full complexity, and preserves it by perfusion for several days outside the body for ex vivo screening and analysis. Partnering with the Melcher lab, we now use explant-in-chip models to investigate how immune stimulants prime an immune response in murine melanoma explants. While explant-in-chip is amenable to many immunopriming treatments (oncolytic viruses, STING agonists, etc.), we focus on radiotherapy as an immunogenic treatmenrt, because it is the expertise of the Melcher lab and is highly relevant to clinical application.

Literature references

*Wilkins A, Fontana E, Nyamundanda G, et al. Differential and longitudinal immune gene patterns associated with reprogrammed microenvironment and viral mimicry in response to neoadjuvant radiotherapy in rectal cancer. Journal for ImmunoTherapy of Cancer 2021;**9**:e001717. doi:10.1136/ jitc-2020-001717*

Person specification

This project is suitable for a talented graduate or undergraduate student with life sciences, engineering, or physics background. The standard minimum entry requirement is a relevant undergraduate honours degree (First or 2:1). Applications are invited from talented graduates or final year undergraduates. We particularly welcome British applicants from Black and ethnic minority backgrounds, as they are underrepresented at PhD level within Imperial and The Institute of Cancer Research.

The studentship will be registered at the Institute of Cancer Research with affiliate status at Imperial College London. The student will have access to both institutions and benefit from the world class research infrastructure and expertise across the two institutions. The student will become a member of the CRUK Convergence Science Centre PhD cohort which is a unique group of students working across distinct disciplines to tackle the big problems in cancer. A unique convergence science training programme will provide the skills and language to navigate different disciplines.

Funding and Duration

Studentships will be for four years commencing in October 2022. Successful candidates will undertake a four-year research training programme under the guidance of a supervisory team of world-class researchers. Students will receive an annual stipend, currently £21,000 per annum, and project costs paid for the four-year duration. Convergence Science PhDs cover tuition fees for UK students only. Funding for overseas fees is not provided, international students are invited to apply subject to outlining how they will meet the difference in tuition fees.