Engineering next generation targeted cancer immunotherapy

Supervisors:

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Project outline

Checkpoint inhibitors (CPIs) targeting PD1 and CTLA4 achieve ~11% of cure rates in advanced melanoma. However, treatment response rates remain low for the majority of cancer types. CPI therapy does not exhibit strong antitumour response in tumours with few immune cells. One way to improve CPI efficacy is to induce inflammation within the tumour by enhancing recruitment and infiltration of tumour-specific immune cells into the tumour. However, to reduce toxicities, it is crucial to induce localised inflammation only within tumour and not in systemically in body. The Ishihara laboratory utilises immunoengineering strategies to develop novel protein based technologies to achieve tumour-specific delivery of immunotherapeutics, focusing on unique extracellular matrix (ECM) targeting approaches. In partnership with the Huang laboratory who has expertise in sarcoma tumour biology, ECM biology and proteomics, this project will engineer therapeutic strategies that harness the ECM as a means to rationally modulate the cancer immune microenvironment which represents a completely new class of convergence therapeutics. Ishihara and Huang labs have identified new target ECM protein in cancer. Utilising phase display technology, the Ishihara lab has developed a range of different Fab (antigen binding fragment) antibodies that target tumour specific ECM.

Hypothesis

We hypothesise that this tumour-specific ECM presents a unique opportunity for targeted delivery of drugs and immunomodulatory cytokine payloads for cancer therapy. By employing matrisomal analysis of soft tissue sarcomas, the Huang laboratory has shown that selected histological subtypes display upregulated levels of this ECM protein. In this project, we will utilise sarcomas as a cancer model to engineer next generation antibodies for targeted delivery of immunomodulatory agents for use in cancer immunotherapy.

Importance

Unlike conventional biotherapeutic strategies for antibody drug development, this project is novel in that it exploits immunoengineering as means to directly target a unique aspect of cancer biology (the ECM) that has in the last two decades been largely deemed undruggable. Previous efforts in this therapeutic space (for instance blocking integrin-ECM interactions) have failed. Ishihara's unique approach to deliver immunotherapeutics to cancer ECM matrices is evidenced by 5 previous papers (Sci Transl Med 2017 and 2019, Nat Biomedical Eng 2020, Sci Adv 2019 and 2019). Importantly, our targeting drug delivery

strategy may improve the safety of untargeted systemic cancer drugs, including agents that have previously failed in the clinical trials due to unacceptable toxicity, such as IL-12.

This project will encompass 3 aims:

Engineering and in vitro characterisation of antibody-cytokine conjugates.
The student will engineer antibody-cytokine conjugates including immunomodulatory agents. The Ishihara lab has extensive experience in generating such ECM targeting agents (Ishihara et al., Nat Biomed Eng 2020, Sci Transl Med 2019, Sci Transl Med 2018, Sci Adv 2019), and has shown that these targeted cytokines and chemotherapeutic agents have utility in activating the immune system in cancer models with synergistic activity when used in combination with immune checkpoint inhibitors.

Evaluate the efficacy of ECM targeting candidate agents in 3D co-culture models of sarcoma
The ECM targeting agents from Aim 1 will be evaluated in a semi-high throughput fashion in the 3D models developed in the Huang lab for the ability to bind to patient-derived ECM hydrogels, kill primary sarcoma tumour cells and activate immune cells.
Test the most active ECM-targeting agents for therapeutic efficacy in mouse models of sarcoma
In this aim, the student will use genetically engineered and syngeneic mouse models of sarcomas to test the most effective ECM-targeting agents identified in Aim 2. This will include evaluation of tumour size, proliferative and necrosis markers, systemic toxicity, and immunological analyses.

Literature references

1. Ishihara, et al., Targeted antibody and cytokine cancer immunotherapies through collagen affinity. Science Translational Medicine, 11, eaau3259, 2019
2. Mansurov, A., Ishihara, et al., Collagen-binding IL-12 enhances tumour inflammation and drives the complete remission of established immunologically cold mouse tumours. Nature Biomedical Engineering, 2020.
3. Ishihara, et al., Matrix-binding checkpoint immunotherapies enhance anti-tumor efficacy and reduce adverse events. Science Translational Medicine, 9, eaan0401, 2017
4. Ishihara, et al., Recruitment of CD103+ DCs via tumor-targeted chemokine delivery enhances efficacy of checkpoint inhibitor. Science Advances, 5, aay1357, 2019
5. Sasaki and Ishiahra et al., Engineered collagen-binding serum albumin as a drug conjugate carrier for cancer therapy Science Advances, 5, aaw6081, 2019

Key Words

1. Cancer immunotherapy
2. Drug development
3. Tumour matrisome
4. Sarcoma
5. Protein Engineering
6. ECM targeting

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) and our full eligibility criteria can be found here: https://www.icr.ac.uk/studying-and-training/phds-for-science-graduates/entry-requirements

The studentship will be registered at Imperial College London with affiliate status at the Institute of Cancer Research. 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 2021. Applications for PhDs are invited from talented UK graduates or final year undergraduates. International students are also invited to apply subject to outlining how they will meet the difference in tuition fees.

We look forward to receiving applications from all candidates and will select those who display the potential to become the world leading cancer researchers of the future based on their application and performance at interview. However, we are particularly to welcome UK applicants from Black and ethnic minority backgrounds, as they are underrepresented at PhD level within the ICR and Imperial.

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.