Project Title: “Study the mechanisms that couple host detection of commensal microbes and tissue damage to cancer immunity”

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Research Group: Cancer Immunosurveillance

The immune system has been sculpted by evolution to constitute a natural host defence mechanism to life-threatening insults. Although mainly studied in the context of infectious diseases, it is now precedent that the immune system can detect and eradicate malignant cells, thus inhibiting cancer formation. Remarkably, immunotherapies have dramatically improved clinical outcomes in patients with advanced cancers. Nevertheless, there is significant heterogeneity in response rates and durable clinical benefits are limited to a small subset of patients. Resistance to immunotherapies is often attributed to blunted immune cell reactivity against cancer. Therefore, deciphering the mechanisms that govern cancer immunity is of paramount importance to improve immunotherapy and overcome resistance.

In the Cancer Immunosurveillance group (www.cruk.manchester.ac.uk/Our-Research/Cancer-Immunosurveillance), we combine genetically modified mouse models and tumour engineering to disentangle complex tumour-host interactions that underpin cancer immunity. We have previously shown that immune detection of dying tumour cells can elicit anti-cancer immunity. We have characterised the mechanisms that couple recognition of dead-cell-associated signals to cytotoxic T cells responses and identified molecules of the host that act as natural barriers of cell death sensing, inhibiting anti-cancer immunity (Giampazolias et al Nature Cell Biology, 2017, Giampazolias et al Cell Cycle, 2018, Giampazolias et al Cell, 2021, Lim KHJ et al JTC, 2022). Interaction of dying cancer cells with the immune system is necessary but not sufficient to elicit cancer immunity due to the requirement of immunological permissive environments dictated by the gut microbiome. However, how the gut-resident microbes are regulated and modulate immune responses to cancer remains unclear. Intriguingly, we recently found that the prevalence of a specific micronutrient and its interaction with host components tune the integration of gut-associated microbial signals to the immune system, acting as determinant of anti-cancer immunity (Giampazolias* et al in revision, *Corresponding author).

The aim of this project is to characterise the mechanisms that enable the immune system to recognise and respond to cancer through sensing and integration of cues that are elicited by dying cells and commensal microbes. The successful candidate will be trained in state-of-the-art facilities in the use of in vivo animal models, cell engineering and cell analysis techniques (flow cytometry and microscopy). Our Institute hosts the largest concentration of scientists, clinicians and operational staff in Europe and is part of the Manchester Cancer Research Centre – a highly successful partnership between 3 powerhouses of innovation, The Christie, Cancer Research UK and The University of Manchester. We welcome talented graduates with enthusiasm for scientific research into the fundamental principles of cancer immunity.

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