Project title: “The COX-2/PGE\(_2\) axis: a dominant inflammatory pathway that enables cancer immune escape and immunotherapy resistance”

Group Leader: Santiago Zelenay

Research Group: Cancer Inflammation and Immunity

Immunotherapies based on antibodies that target T cell-immune checkpoints have transformed the landscape of cancer treatment across multiple tumour types. These immune checkpoint blockade (ICB) therapies can promote remarkable, long-lasting responses in both patients with late-stage cancers or in (neo)adjuvant settings. However, most patients derive only transient or no benefit, and many face harmful side effects. Solutions to these clinical problems require improved fundamental understanding of the principles that govern anti-cancer immune responses. Our group at the Cancer Research UK Manchester Institute investigates the signals and pathways that dictate the establishment of tumour inflammatory environments that promote or restrain the anti-tumour function of the immune system. Using genetically engineered mouse lines with select immune and inflammatory alterations, syngeneic models of cancer and analysis of patient samples, we have uncovered the cyclooxygenase (COX)-2/prostaglandin E2 (PGE\(_2\)) pathway as a nodal inflammatory axis that drives immune evasion (Zelenay et al Cell 2015, Bonavita et al Immunity 2020, Pelly et al Cancer Discovery 2021, Bell et al Nature communications 2022). This PhD project will build upon these findings to deepen our understanding of the mechanisms that regulate the establishment and maintenance of tumour inflammatory environments that either stimulate or hinder immune-mediated tumour control. Central project aims will be to investigate the underlying signalling that regulates COX-2/PGE2 activity by tumour and tumour-infiltrating immune cells and to unravel its specific contribution to cancer inflammation, immunity and tumour fate.

We welcome applications from individuals with a strong academic track record with previous laboratory research experience.

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