DEPARTMENT OF BIOTECHNOLOGY

pCoE Cancer Genomics and Molecular therapeutics

BIO GROUP SEMINAR SERIES

Seminar by

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Natural barriers of cancer immunity :*Unmasking cancer through self-deception*

The immune system constitutes a natural host defence mechanism to life-threatening insults. Although, mainly studied in the context of infectious diseases, it is now precedented that the immune system can inhibit cancer formation by detecting and eradicating malignant cells. Immune checkpoint blockade (ICB) therapy restores T cell immunity to cancer cells and represents the pinnacle of success for treating patients with advanced cancers. Despite the substantial achievement in clinical care, only a small fraction of patients receiving ICB therapy results in durable responses. The solution to overcome resistance to ICB therapy will stem from the fundamental understanding of the origin of cancer-specific T cell responses.

What triggers T cell immunity to cancer?

When do cancer-specific T cell responses fail to be triggered?

Cancer has been described as *"wound that never heals"* due to the constant presence of cell death in the tumour microenvironment triggered by anti-cancer therapy, cellular stress, and limited availability of survival factors, such as nutrients and oxygen. We found that specialized dendritic cell (DC) subsets mount cancer-specific T cell responses through sensing and integration of cues that are elicited by dying tumour cells. We further identified intracellular (caspases) and extracellular (secreted-gelsolin) molecules of the vertebrate host physiology acting as natural barriers to cell death sensing and cancer immunity. Highlighting the therapeutic potential, inhibition or genetic deletion of these molecules boosted spontaneous immunity to cancer and significantly augmented the response to ICB and other anti-cancer therapies in preclinical models, whereas their high prevalence in human cancers inversely correlated with patient overall survival (Giampazolias et al. *Nature Cell Biology*, 2017, Giampazolias et al. *Cell*, 2021 and Lim KHJ et al. JITC, 2022).