Durable T cell reprogramming in anti-PD1 therapy: single-cell mechanisms and biomarkers of response

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Project Summary: CD8+ T cells are central to anti-cancer immunity, but their activity is limited by the inhibitory receptor PD1. Anti-PD1 antibodies, such as pembrolizumab, enhance T cell function and yield durable clinical responses in some patients, yet responses are variable and the molecular determinants of long-term benefit remain unclear. Current methods to measure PD1 receptor occupancy (PD1RO) provide only population-level estimates, obscuring cell-to-cell variability that may predict patient outcomes. This project aims to address these gaps through a combination of single-cell immunology and mathematical modelling.

We will first develop a novel assay to quantify PD1RO at the single-cell level using spectral flow cytometry. We will then use modelling approaches to estimate receptor occupancy robustly, accounting for variation in receptor density and single-cell measurement uncertainty.
Using clinical samples from the UK multicentre REFINE-Lung and REFINE-Renal cancer immunotherapy trials, as well as ongoing trials in head and neck cancer, we will test whether PD1RO early during treatment predicts patient outcomes. By integrating estimates of occupancy and uncertainty into Cox survival models, we aim to identify whether early or on-treatment PD1RO can serve as a predictive biomarker.

Finally, we will investigate whether T cells that were once drug bound retain features of enhanced effector function after drug dissociation. Using longitudinal multi-omic single-cell profiling, receptor occupied and unoccupied T cells will be tracked over time. By tracking individual T cell clones across treatment, we will determine whether receptor-occupied cells are molecularly "reprogrammed" and whether this imprint correlates with durable clinical benefit.

This project combines cutting-edge single-cell assays, quantitative modelling, and clinical trial samples to address fundamental questions about anti-PD1 therapy. Results will provide mechanistic insight into T cell reprogramming, establish PD1RO as a potential predictive biomarker, and guide strategies to personalise immunotherapy for cancer patients.

Literature references

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Key words: 1 Cancer immunology 2. Cancer immunotherapy
Project suitable for a student with a background in: Life Sciences, Physics or Engineering, Mathematics, Statistics, Epidemiology