

Abstract

- <working title>
 - High-throughput genomic profiling of response to *in vivo* immune perturbations
- <other candidate titles>
 - Transcriptomic response to immune perturbation, and its genetic architecture
 - Characterising immune response to vaccines and drugs using longitudinal *in vivo* study designs
 - Identifying associations with vaccine and drug response in longitudinal studies
 - Systems immunology of *in vivo* vaccine and drug responses

The human immune system plays a central role in defense against infection, but it's dysregulation is implicated in immune-mediated diseases. The past decade has seen increasing application of high-throughput technologies to profile, predict, and understand immune response to perturbation. The ability to measure immune gene expression at scale has led to the identification of transcriptomic signatures that predict clinical phenotypes such as antibody response to vaccines. It has also been recognised that both expression and phenotypic responses are complex traits with their own genetic architecture. This thesis examines the longitudinal transcriptomic response to immune perturbations, and its association with clinical response phenotypes and common genetic variation.

Chapter 2 explores transcriptomic response to pandemic influenza vaccine in a multi-ethnic cohort of healthy adults. The success of vaccination in controlling influenza is indisputable, but it is incompletely understood why some individuals fail to mount protective antibody responses. I meta-analysed blood microarray and RNA-sequencing (RNA-seq) datasets, identifying a distinct transition from innate immune response at day 1 after vaccination, to adaptive immune response at day 7. Heterogeneity between measurement platforms made it difficult to identify single-gene associations with antibody response. Using a gene set approach, I found expression modules related to inflammatory response, the cell cycle, CD4+ T cells, and plasma cells to be associated with vaccine-induced antibody response.

In chapter 3, I map response expression quantitative trait loci (reQTLs) in the same cohort to investigate regulation of transcriptomic response by common genetic variants. Rather than driving differential expression post-vaccination, the strongest reQTL appear to be explained by changes in cell composition revealing cell-type specific expression quantitative trait loci (eQTLs). For example, a reQTL identified for *ADCY3* specific to day 1 was driven largely by

high monocyte proportions at day 14. Changes in cell composition present a significant challenge to the interpretation of reQTLs found in bulk data.

Finally, chapter 4 applies an analogous longitudinal study design to explore Crohn's disease (CD) patient response to anti-tumour necrosis factor (TNF) drugs: infliximab and adalimumab. Anti-TNF treatment has revolutionised patient care for CD, but 20-40% of patients develop primary non-response soon after starting treatment. I identified baseline expression modules associated with primary response, but also significant heterogeneity in these associations between drugs. Expression changes post-treatment in non-responders were largely magnified in responders, suggesting there may be a continuum of response. Distinct expression trajectories identified for responders and non-responders revealed sustained expression differences up to week 54. A set of interferon-related genes were regulated in opposing directions in responders and non-responders, presenting an attractive target for future studies of the biological mechanisms of non-response.