Abstract

- <working title>
  - Genetic mapping of transcriptomic response to *in vivo* immune perturbations
- <other candidate titles>
  - Transcriptomic profiling and genetic mapping of response to in vivo immune perturbation
  - Transcriptomic profiling and genetic architecture of response to in vivo immune perturbation
  - High-throughput genomic profiling of response to *in vivo* immune perturbations
  - 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 traits with complex genetic architectures. 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 not completely 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 transcriptomic associations with antibody response. Using a gene set approach, I found expression modules related to the inflammatory response, the cell cycle, $CD4^+$ T cells, and plasma cells to be associated with vaccine-induced antibody response.

I'm trying to say that the response to immune perturbation is heritable/influenced by genetics.

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 eQTL. For example, a reQTL identified for *ADCY3* specific to day 1 was driven largely by high monocyte proportions at day 1 compared to other timepoints. Changes in cell composition present a significant challenge to interpretating reQTLs found through bulk sequencing of heterogeneous tissues.

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 show primary non-response soon after starting treatment. I identified baseline expression modules associated with primary response, but also significant heterogeneity in associations between the two 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 underlying non-response.

I prefer associations over signatures. Signatures should have had their predictive power quantified.