Project 5: Tracing genetic variant effects across molecular scales in human immune cells

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Understanding how genetic variants alter immune cell function remains a major challenge. Most functional genomics studies have focused on variant effects on gene expression, but genetic effects are not confined to a single molecular layer. They can propagate through transcriptional regulation, alternative splicing, signalling pathways and cellular phenotypes such as cytokine secretion. This project will develop computational approaches to reconstruct these cascades of molecular effects, enabling a more integrated understanding of how genetic variation shapes human immune traits.

The project will leverage a unique dataset generated through the JAGUAR consortium, an international effort to characterise immune responses across diverse Latin American populations. JAGUAR profiles peripheral blood immune cells from healthy individuals sampled across six Latin American countries, creating one of the largest multi-ancestry functional genomics resources in immune biology. Within this resource, approximately 200 individuals of Mexican and Peruvian ancestry have been profiled using matched short-read single-cell RNA-seq, long-read single-cell RNA-seq and multiplex cytokine secretion assays across multiple immune stimulations and time points, generating data from approximately 1,500 samples across 200 genetic backgrounds. Each assay is linked to genome-wide genotype data, enabling systematic investigation of how naturally occurring genetic variation shapes immune responses.

This combination of matched transcriptomic, isoform-resolved and functional phenotyping makes the dataset exceptional. Few resources capture gene expression, RNA isoform usage and secreted immune phenotypes across the same individuals, across multiple perturbations, and at a scale suitable for population genetic analysis. The focus on Latin American populations provides an additional opportunity to address a major gap in functional genomics, where individuals of non-European ancestry remain substantially under-represented.

The Fellow will develop and apply computational methods to integrate these complementary data types and identify latent biological programmes that explain coordinated variation across molecular layers. Building on statistical genetics, latent factor modelling, causal inference and multimodal machine learning, the project will jointly model transcriptional states, alternative splicing and cytokine secretion to identify genetically regulated immune programmes. These

models will enable mapping of regulatory variants acting at different stages of cellular information flow, from transcription and RNA processing through to immune effector function.

A central objective will be to move beyond cataloguing molecular QTLs towards modelling the propagation of genetic effects across linked phenotypes. By combining quantitative trait locus mapping with multivariate and causal modelling approaches, the project will investigate how individual variants influence coordinated cellular responses across modalities and identify molecular intermediates that connect disease-associated genetic variation to immune function. This will provide mechanistic insight into immune disease loci and generate methods broadly applicable to emerging multi-omic population cohorts.

The fellowship brings together complementary expertise from the Wellcome Sanger Institute and EMBL-EBI. The Trynka group has established the JAGUAR consortium and generated the underlying multi-omic datasets, with expertise in human genetics, single-cell genomics and immune biology. The Saez-Rodriguez group is internationally recognised for computational methods in biological network inference, machine learning and multi-omics integration. Together, the collaboration provides an ideal interdisciplinary environment for developing next-generation methods that connect statistical genetics with systems biology and for training an ESPOD Fellow at the interface of genomics, computation and translational immunology.