Decoding morphological programmes of T cell activation through multimodal imaging and machine learning

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Project summary: T cells undergo profound changes in both transcriptional state and cellular morphology during activation. These changes are essential for proper immune function and are tightly regulated over time. While transcriptomic programs have been extensively studied, the corresponding morphological dynamics, especially at high resolution and across diverse perturbations, remain far less explored. There is a pressing need for scalable, interpretable approaches that bridge cell morphology with functional outcomes during immune activation.

To address this gap, the Trynka Group developed Tglow, a high-throughput imaging platform that captures rich, multiparametric data on primary human T cells as they activate over time. Tglow enables us to observe cell behaviour in multiple modalities, including brightfield, and 3D fluorescence, providing an unprecedented view of the physical changes that accompany T cell activation. In parallel, we are actively generating gene perturbation data using CRISPR-based tools, which enables the inference of regulators driving morphological and functional transitions.

Despite the richness of this dataset, there is a lack of robust computational methods and training data to extract, interpret, and organize complex morphological features in a way that is scalable, time-resolved, and biologically meaningful. This project aims to address this gap through one or more of the following directions, to be selected based on the Fellow's expertise and interest:

1. Brightfield phenotyping: brightfield images are fast and non-invasive but underused. Recent deep learning methods can "virtually stain" these images to reconstruct fluorescent labels, revealing how much biological signal is inherently captured. We will train models to predict key morphological markers from brightfield alone, unlocking the potential to monitor activation dynamics continuously and at scale.

2. Supervised phenotype detection: T cells display diverse and sometimes subtle morphologies, such as granular ER, actin distribution, or mitochondrial fragmentation, that are easily seen by eye but hard to quantify. We will train classifiers on a few manually labelled examples, using both CellProfiler features and raw images, to

detect these phenotypes across time and perturbations.

3. 3D feature extraction: Although we acquire full 3D image stacks, most current analyses use 2D projections, potentially missing key spatial features. We will implement and compare 3D vs 2D morphological descriptors to identify phenotypes or patterns uniquely visible in full 3D, particularly in nuclear shape, cytoskeletal architecture, and organelle distribution.

4. Representation learning of morphological programs: To uncover emergent structure in the data, we will apply deep representation learning approaches such as VQ-VAEs. By training models to emphasize biologically meaningful variation (e.g., activation state) while minimizing the impact of technical noise (e.g., donor batch), we aim to learn latent morphological features that are predictive of T cell function.

The Trynka lab offers strengths in T cell biology, human genetics, and functional genomics, along with access to rich datasets from activation time courses and CRISPR perturbations in primary human T cells. The Ewald lab contributes expertise in machine learning for biological images, including interpretable deep learning and representation learning for cell morphology. This new collaboration will provide the Fellow with integrated training across experimental imaging, computational modeling, and immune cell biology, supported by strong mentorship from both labs.

Scientific & professional training: At the **Sanger Institute**, the Fellow will receive hands-on training in high-content microscopy, primary human T cell culture, and CRISPR-based screening, along with experience in large-scale imaging experiment design and data curation. At **EMBL-EBI**, they will learn state-of-the-art computational methods for image analysis, including feature extraction, supervised learning, multimodal data integration, and deep learning methods such as VQ-VAEs and contrastive learning. The Fellow will take part in joint lab meetings, seminars, and conferences, with regular opportunities to present their work. They will contribute to collaborative publications and open-source code, and participate in formal training programs at both institutes.

Potential for new research directions: This project offers substantial potential for exploring new directions, such as cross-cell-type phenotyping tools, integrating imaging with other omics, unsupervised cell state discovery, and translational applications in drug response or patient stratification. The combination of deep experimental data and advanced modelling will provide a strong foundation for an independent research career in quantitative biology and biomedical AI.