Targeted Project / AY 2025 -2026

Intrinsic and extrinsic control of T cell migration

Project Reference: TRG-BAB-AR

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Co-supervisor: Dr Gosia Trynka (Sanger Institute)

BBSRC DTP main strategic theme: Understanding the rules of life

BBSRC DTP secondary strategic theme: Transformative technologies, Bioscience for an integrated understanding of health

Project outline:

Cellular migration is a critical function of immune cells that is required for optimal host protection. Directed migration is achieved by a combination of local- and distal-acting signals, in concert with gradient-sensing and motility-directing intracellular machinery. Movement of activated T cells between lymph node environments and into inflamed tissues is key to generating a differentiated T cell response and targeting that response toward the site of pathogen invasion. Defects in lymphocyte migration have been associated with age-related immune response decline, and a better understanding of the mechanics of T cell migration may identify pathways for further investigation in an aged setting.

This project will compare the molecular regulators of directed migration in human CD4 and CD8 effector T cells to study how cell-intrinsic pathways, cell-extrinsic factors and feedback loops facilitate localization of these similar but functionally distinct cell types. Specifically, we will examine the molecular underpinnings of how T cells respond to, and even generate themselves, chemotactic signals. We will use a combination of in vitro cellular assays, advanced imaging, and CRISPR/Cas9 manipulation of genes involved in signalling and motility. This project is a collaboration between the Richard Lab at the Babraham Institute and the Trynka Lab at the Sanger Institute and will leverage their respective expertise in immune cell assays and CRISPR/Cas9 technology.

The student will have the opportunity to work in two academic institute settings (Babraham and Sanger), where they will benefit from highly collaborative environments with collective expertise in Immunology, Genomics, Signalling, and Epigenetics. They will be involved in all aspects of project planning, experimentation and analysis, with support from other team members. Training will be provided in immunological and genome editing techniques and analyses, including functional secretion and chemotaxis assays, CRISPR/Cas9-mediated knockout and overexpression systems, advanced imaging and flow cytometry. The student will have the opportunity to share their research through publications and presentations at internal meetings and external conferences.

References:

Richard AC, Ma CY, Marioni JC, Griffiths GM. (2023) Cytotoxic T lymphocytes require transcription for infiltration but not target cell lysis. EMBO Rep, 24:e57653.

Ma CY, Marioni JC, Griffiths GM, Richard AC. (2020) Stimulation strength controls the rate of initiation but not the molecular organisation of TCR-induced signalling. Elife, 9:e53948.

Soskic B, Can-Gamez E, Smyth DJ, Ambridge K, Ke Z, Matte JC, Bossini-Castillo L, Kaplanis J, Ramirez-Navarro L, Lorenc A, Nakic N, Esparza-Gordillo J, Rowan W, Wille D, Tough DF, Bronson PG, Trynka G. (2022) Immune disease risk variants regulate gene expression dynamics during CD4+ T cell activation. Nat Genet, 54(6):817.

Keywords: T cells, CD4, CD8, Migration, Chemotaxis, CRISPR screen