Functional Genomics Doctoral Landscape Award (FGx-DLA)

PROJECT TITLE: Functional genomics of organelle communication networks controlling human β-cell maturation

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Project details

Our cells depend on highly organised communication networks between intracellular organelles. Many of these interactions occur at membrane contact sites, where organelles exchange signals, calcium and metabolites without fusing. In pancreatic β-cells, this communication must be precisely regulated to coordinate glucose sensing, energy production, calcium dynamics, lipid metabolism and insulin secretion. However, we do not know how these networks are genetically programmed as β-cells develop and which features distinguish mature from immature networks.

This question is important for both type 1 (T1D) and type 2 diabetes (T2D). Human pluripotent stem cells can now be differentiated into insulin-producing β-like cells with considerable potential for cell replacement in T1D, but incomplete functional maturation remains a major challenge, as these cells do not fully reproduce the sophisticated metabolic and signalling integration of primary β-cells. In T2D, progressive loss of β-cell function and resilience contributes to failure to maintain glucose homeostasis. Understanding how healthy β-cell architecture and organelle communication are established could reveal strategies to generate better replacement cells for T1D and identify mechanisms that maintain endogenous β-cell function in T2D.

We hypothesise that acquisition of mature β-cell identity requires coordinated remodelling of organelle communication networks, and that the genes controlling this process can be discovered through high-content functional genomics.

The student will first establish a quantitative atlas of organelle organisation during human stem cell differentiation into β-cells, initially focusing on communication between the endoplasmic reticulum (ER), mitochondria and peroxisomes. Genetically-encoded membrane contact site reporters and Cell Painting will generate multidimensional phenotypic profiles across developmental stages. These will be integrated with measurements of β-cell function, including glucose-stimulated insulin secretion, calcium signalling and mitochondrial metabolism. Mature human and mouse primary β-cells will provide a physiological benchmark for features associated with successful β-cell maturation.

CRISPR-based genetic perturbation combined with automated high-content microscopy will next identify genes whose manipulation shifts immature cells towards, or away from, the organelle architecture and interaction networks of mature β-cells. Quantitative image analysis will enable the identification of genetic regulators of organelle communication at different stages of β-cell

maturation. Transcriptomic and chromatin accessibility profiling will provide complementary information linking selected phenotypes to underlying gene regulatory programmes.

Selected candidate regulators will then undergo mechanistic validation using focused CRISPRi/CRISPRa perturbation, organelle contact site imaging and functional β-cell assays. Particular attention will be paid to ER-mitochondria and ER-peroxisome communication, while retaining scope for the student to pursue unexpected genes and pathways emerging from the screen.

The project is intrinsically interdisciplinary, integrating human stem cell and β-cell biology, functional genomics, genome engineering, high-content microscopy and computational phenotyping, drawing on complementary expertise across the Tomas and Child laboratories and the London Biofoundry. The student will receive training spanning experimental and computational biology, from designing reproducible functional genomic screens to mechanistic validation of individual hits.

The project will generate a functional genomic map linking gene perturbation to organelle architecture, β-cell maturation and function. By identifying causal regulators of β-cell maturation, it could uncover pathways for generating more mature and resilient replacement β-cells for T1D, while revealing fundamental mechanisms governing β-cell dysfunction in T2D.

Relevant publications

1. Austin et al., GLP-1R associates with VAPB and SPHKAP at ERMCSs to regulate β-cell mitochondrial remodelling and function. Nature Communications 2025 Dec 10;16(1):11010 https://doi.org/10.1038/s41467-025-66115-x

2. Buenaventura et al., A Targeted RNAi Screen Identifies Endocytic Trafficking Factors that Control GLP-1 Receptor Signaling in Pancreatic Beta Cells. Diabetes 2018 Mar;67… https://doi.org/10.2337/db17-0639

3. Das et al., CORe Designer: a CRISPR design tool for proteome engineering. bioRxiv 2026.06.12.731864; doi: https://doi.org/10.64898/2026.06.12.731864

Please direct project-specific enquiries to:

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How to Apply

IMPORTANT: Please note that this is a two-stage application. Please ensure you read the entry requirements for the programme you are applying for.

Please complete the following steps:

1. To apply for this project please click on the following link. Please make a note of your Student Applicant ID number. APPLY HERE

2. Complete the Student Application Questionnaire. You will need your Student Applicant ID to complete this. Student Application Questionnaire – Fill in form