Decoding Pathological Immune Memory to Mend the Metabolically Stressed Heart

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Project Description:

- **The Challenge:** Heart attack remains a leading cause of death, and patients with common metabolic disorders like obesity and dyslipidaemia face worse prognosis, often leading to heart failure. Current treatments fail to address the underlying reasons for this impaired cardiac repair. Our pilot study reveals a startling insight: the cardiovascular system in obese individuals is already in a pre-conditioned state of chronic stress, exhausting its reparative capacity before an injury even occurs. This project tackles the fundamental question: how does chronic metabolic stress reprogram the immune system to sabotage healing?
- **The Hypothesis:** We propose a novel mechanism: dyslipidaemia creates a form of 'pathological innate immune memory' in a key population of cardiac immune cells—the macrophages. We hypothesise that metabolic dysfunction rewires the epigenome of these critical cells, locking them into a dysfunctional state that impairs their ability to orchestrate effective repair following a heart attack.
- **The Project:** This project will take you on a complete scientific journey from in vivo functional discovery to deep, cross-species mechanistic investigation. You will:
    1. Employ cutting-edge zebrafish models of diet-induced obesity and cardiac injury to establish the causal link between macrophage metabolism and repair outcomes *in vivo*.
    2. Spearhead the generation of a cross-species multi-omics atlas. You will integrate state-of-the-art single-cell genomics (snRNA-seq, snATAC-seq) from both our zebrafish model and human cardiac tissue to map the epigenetic blueprint of macrophage dysfunction.
    3. Master advanced bioinformatics to build a 'Cross-Species Target Prioritization Funnel', integrating these complex datasets to identify a short-list of high-confidence, human-relevant genes and pathways that drive pathological immune memory.
- **Training and Environment:** This project offers exceptional, multi-disciplinary training at the cutting edge of immunometabolism, epigenetics, and cardiovascular biology. You will be trained in a highly sought-after research pipeline, including advanced microscopy, zebrafish genetics, single-cell multi-omics, and the complex cross-species bioinformatic analysis required to integrate them. You will join a dynamic and collaborative team and be embedded within the interdisciplinary environment of the Living Systems Institute (LSI), working alongside leading biologists, physicists, and mathematicians to solve complex biological problems. This project provides an excellent opportunity to conduct fundamental discovery science aimed at identifying novel therapeutic targets, preparing you for an impactful career in academic or industrial cardiovascular research.