Internship Proposal

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Project Title:
Decoding the Endocrine Pancreas Regulome and Its Implications in Type 2 Diabetes Development

Level:

Master Student

Project Summary:

Mutations in non-coding DNA are likely major contributors to susceptibility to Type 2 Diabetes (T2D). Understanding how these variants affect endocrine pancreas function is therefore crucial for uncovering the molecular mechanisms underlying T2D development (1). However, in vivo models that directly link non-coding mutations to changes in gene expression and pancreatic function remain limited (1,3).

This project aims to investigate how combinations of mutations in transcriptional enhancers active in the endocrine pancreas affect pancreatic function and contribute to diabetes-like phenotypes. Using zebrafish as a vertebrate model, the project will explore how alterations in the regulatory landscape of the endocrine pancreas influence gene expression and glucose homeostasis.

Work to be developed by the student:

The student will use targeted mutagenesis to disrupt approximately 50 endocrine pancreas enhancers previously identified as important regulators of pancreatic function. The project will involve generating and maintaining mutant families, identifying animals carrying combinations of enhancer mutations, and assessing the impact of these mutations on glucose homeostasis and endocrine pancreas function.

The student will receive training in zebrafish genetics and husbandry, CRISPR/Cas9-mediated genome editing, molecular biology techniques including multiplex PCR and next-generation sequencing, analysis of sequencing data, and methods for measuring glucose levels in zebrafish tissues.

Specifically, the student will:

1) Design and validate sgRNAs targeting multiple endocrine pancreas enhancers in zebrafish.

2) Generate, maintain, and genotype zebrafish lines carrying regulatory mutations.

3) Characterize combinations of enhancer mutations and correlate genotype with alterations in glucose homeostasis.

4) Contribute to the identification of regulatory elements whose disruption leads to diabetes-like phenotypes.

This project will provide hands-on training in functional genomics, gene regulation, zebrafish genetics, and diabetes research while addressing fundamental questions about the contribution of non-coding variation to complex disease.

References:

1-Bordeira-Carriço, R. et al. Cis-regulatory similarities in the zebrafish and human pancreas uncover potential disease-related enhancers. Nature Communications13(1):, 2022. doi: 10.1038/s41467-022-29551-7

2-Eufrásio, A. et al. In Vivo Reporter Assays Uncover Changes in Enhancer Activity Caused by Type 2 Diabetes-Associated Single Nucleotide Polymorphisms. Diabetes. 69, 2794–2805 (2020).

3-Amorim, J. P. et al. A Conserved Notochord Enhancer Controls Pancreas Development in Vertebrates. Cell Rep. 32, 107862 (2020).

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