INTERDISCIPLINARY GRADUATE PROGRAM IN

MOLECULAR AND CELLULAR BIOLOGY

DISSERTATION SEMINAR

Graph Theory Analysis of Single Cell Transcriptomes Define Islet Signaling Networks and Cell Identity

Scott Tyler
PhD Candidate

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2117 Medical Education Research Facility (MERF)

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Single-cell RNAseq (scRNAseq) offers a remarkably detailed look into the transcriptional regulation of the genome. While this technique has increased our appreciation for the heterogeneity in cellular populations, the complexity revealed also makes it difficult to translate scRNAseq into intuitively meaningful results. We created a new informatics tool (PyMINEr) to address these challenges. Using scRNAseq data from human islets, we tested the robustness PyMINEr to define transcriptional networks that control cellular identity, paracrine/autocrine signaling relationships between 8 islet cell types, and new potential functional roles for type 2 diabetes (T2D)-associated genes within islet-associated cell types. Using graph theory principles in PyMINEr, we discovered that weakly expressed genes with high network connectivity (i.e., detectable correlations) are significantly enriched with cell type-specific genes that likely contribute to cell identity. By integrating ChIP-seq data into this analysis, we demonstrate that the graph structure representing transcription was highly dependent on the proximity of promoter transcription factor binding sites within coordinately-regulated target genes. To validate the network of transcriptional relationships discovered by PyMINEr, we interrogated the temporal changes in beta cell transcription following knockdown of Pdx1 and NeuroD1, which shared neighboring genes in the graph model of beta cells. Inhibition of these transcription factors activated components of the alpha-cell program, while also repressing the beta cell program. These bioinformatics approaches demonstrate that network graph analyses at the single-cell level can provide important insights into genome structure, the pathways that control transcriptome regulation and cellular identity, as well as build a framework for understanding the pathology of disease-associated loci.

Scott Tyler
Biographical Sketch

In high school Scott received a letter from himself written in the third grade. As it turned out third grader Scott had ambitions to become a hockey goalie in the NHL. However, by the end of high school, science, and keeping all of his teeth had become larger interests.

In his undergraduate years at West Chester University of Pennsylvania, Scott did research on green mechanochemistry in Dr. Joel Resner's lab. This included valuable lessons including learning to clean dishes, but also learning to be independent and creative in the lab. His final lesson in undergraduate research included the important knowledge that it takes more than four days and 75 cups of coffee to write a thesis (although technically possible).

Between undergraduate and graduate school, Scott worked as a research assistant in at Children's Hospital of Philadelphia with Dr. John Maris' lab studying a pediatric cancer called neuroblastoma. Following that, he moved to Iowa to study molecular and cellular biology.

After learning to handle the smell of ferrets, he enjoyed many collaborations and a freedom of intellectual exploration in Dr. John Engelhardt's lab. Scientists are perpetually reminded of the need for humility. Scott learned this early on in John's lab, but eventually found a niche in bioinformatics.

DISSERTATION COMMITTEE

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