2021 Postdoc Research Symposium
12-Minute Research Talks
Interdisciplinary Biomedical Sciences: Abstract Book

1. **Dr. Anne Talkington, Biomedical Engineering, Systems Immunology. "Assessing treatment-resistant cancers through cellular interaction networks."**

While targeted therapies and immunotherapies hold some success as late-stage cancer treatments, patient-specific responses vary. Pharmacogenomic approaches have greatly advanced our understanding of differential responses to treatment based on large gene expression datasets. These approaches hold even greater potential with the advent of single- cell RNA sequence analysis (scRNA-seq). I plan to leverage the resolution of single-cell data byconsidering gene expression in the context of a cellular interaction network. By doing so, I propose to use scRNA-seq data to identify intercellular communication processes contributing tothe resistance of melanoma in treatment non-responders. To accomplish this, I will first construct an interaction network for the tumor microenvironment based on publicly available datasets, and then correlate the network with the phenotype of response to therapy. Next, I will assess the role of glycosylation, a post-translational modification that has been associated with the aggressiveness of cancer and in known to modulate cell-cell interactions. Ultimately, I aim toapply *in silico* models for testing the impact of new targeted therapies on the prognosis of a patient's digital twin, and thus suggest a treatment strategy for traditionally resistant cancers with clinical utility.

2. **Dr. Cameron Griffiths, Biomedical Engineering, Systems Virology. "Defining roles for distinct cardiomyocyte adaptations to chronic viral infection"**

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Purpose: Several viruses can infect the human heart, causing inflammation known as viral myocarditis. Although most cases of viral myocarditis are self-limiting, some persist in a chronic state. Chronic myocarditis leads to a disease called dilated cardiomyopathy (DCM), which is characterized by a large, weakened heart. The only treatment for DCM is heart transplant. Cells

can adapt to chronic infection by changing their gene expression. However, it is unknown howcardiac cells adapt to chronic infection and why only some infections progress from acute to chronic.

Methods: Unmapped RNA-sequencing reads from four publicly available datasets, consisting of 1026 healthy and DCM patient heart samples, were used to identify undiagnosed heart infections. Differentially expressed genes between virus-positive and virus-negative sampleswere identified and gene set enrichment analysis was used to examine patterns of gene expression specific to virus-positive samples. In parallel, twelve clonal cardiac cell lines wereengineered to express low levels of Coxsackievirus B3, which is a virus known to cause myocarditis. Using RNA-sequencing data, the clones were grouped into three clusters based on similar gene expression.

Results: We detected cardio-pathogenic viruses in 21.6% of the patient-derived samples. Wethen found that in each dataset the virus-positive samples had one of three unique gene expression profiles: increased inflammation, increased cell-cycle associated genes, or decreased AU-rich elements. Similarly, when we examined the chronic clones, each cluster had a gene expression profile that lined up with one of the profiles identified in the patient-derived datasets.

Impact: Each of the gene expression profiles represents a mode cellular adaptation to chronic viral heart infection. Coupled with the patient-derived data, the chronic clones can be used to directly study these cellular adaptations. This project provides insight into what is sustaining chronic viral infection and may lead to interventions to halt the progression to heart failure.

3. **Dr. Matthew Jenior, Biomedical Engineering. "A Systems-Ecology Approach to Engineer Targeted Bacteriotherapy Against C. difficile Infection."**

Clostridioides difficile has become the leading single cause of hospital-acquired infections. Transfer of fecal material from healthy donors (FMT) has been shown to rapidly resolve recurrent *C. difficile* infection (rCDI), restoring the structure and metabolism of the microbiome to a resistant state. Furthermore, numerous studies have demonstrated the importance of specific metabolic pathways in aspects of *C. difficile* pathophysiology, from initial colonization to regulation of virulence factors. In the past, genome-scale metabolic network reconstruction (GENRE) analysis of bacteria has enabled systematic investigation of the genetic and metabolic properties that contribute to downstream virulence phenotypes. With this in mind, we generated and extensively curated *C. difficile* GENRE for a recently characterized hypervirulent isolate (str. R20291). *In silico* exploration of context-specific metabolism during both *in vitro* growth and infection revealed consistent patterns of metabolism which corresponded with experimentally measured increases in virulence factor expression. Next, leveraging human metagenomes from both successful and failed FMT for rCDI, I identified

additional core metabolic properties and microbial species present associated with successful FMT. With these discrete species in hand, I then simulated competition between limited bacterial consortia and *C. difficile* to define patterns of co-metabolism that most corresponded with infection resolution. Highly competative consortia *in silico* were then verified *in vitro* against *C. difficile* growth, and tested in an animal model of CDI revealing concerted depletion of *C. difficile* growth substrates and significant shifts in the course of *in vivo* infection. This work lays the groundwork for understanding novel metabolic control mechanisms of infection present in FMT, and augments future design of targeted probiotics against rCDI.

4. **Dr. Roza Przanowska, Biomedical Engineering, Molecular Biology. "Distinct MUNC lncRNA structural domains regulate transcription of different promyogenic factors."**

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Many long non-coding RNAs (lncRNAs) have been discovered using transcriptomic data, however, it is broadly unclear what fraction of lncRNAs is functional and what structural properties affect their phenotype. *MUNC* lncRNA, also known as ^{DRR}eRNA, stimulates skeletal muscle differentiation and has two isoforms: spliced and unspliced. *siMUNC* reduces myoblast differentiation, and stable over-expression stimulates promyogenic RNAs. *MUNC* is also one of the evolutionary conserved lncRNA and its homolog can be found in human muscles.

The prevailing hypothesis is that *MUNC* stimulates the *Myod1* gene *in cis* as an enhancer RNA and stimulates expression of several other promyogenic genes *in trans* by recruiting the cohesin complex to their promoters. To analyze the functional similarities and differences between the *MUNC* two isoforms, we performed genomic transcriptome profiling (RNA-seq) on myoblasts overexpressing *MUNC*. We showed that both *MUNC* isoforms regulate different sets of genes that are important for the same promyogenic pathways. Experimental probing of the RNA structure by SHAPE-MaP revealed that

MUNC contains multiple structural domains not detected by RNA structure prediction algorithms in the absence of experimental information. We discovered that these specific and structurally distinct domains are required for induction of different promyogenic genes, for binding at different genomic sites to regulate the expression of adjacent genes, and for binding the cohesin complex. We also determined that these phenotypes are primarily driven by the structure with little or no input from the sequence. Moreover, we found that induction of *Myod1* or interaction with cohesin comprise only a subset of the broad regulatory impact of this lncRNA.

Our study thus reveals unexpectedly complex, structure-driven functions for the *MUNC* lncRNA and emphasizes the importance of experimentally determined structures for understanding structure-function relationships in lncRNAs.