Institute for Systems Genomics Networking Workshop

Thursday, November 29, 2018
8:30am – 2:45pm

Wilbur Cross North Reading Room
233 Glenbrook Road
Storrs, CT
Thursday, November 29, 2018

8:30AM - Registration

9:00-9:10AM - Welcome/Introductory Remarks
Provost Craig Kennedy, University of Connecticut

9:10-9:20AM - Challenges and Opportunities in Metagenomic and Metatranscriptomic Profiling of Mouse Gut Microbiota
Mark Adams, Ph.D., The Jackson Laboratory for Genomic Medicine

9:23-9:33AM - Genetics in Weight Loss and Dietary Intake
Jeanne McCaffery, Ph.D., University of Connecticut

9:36-9:46AM - Application of Targeted Screening Approaches to Advance Understanding of RNAbp Roles in Endothelial Regulation of Inflammation
Patrick Murphy, Ph.D., University of Connecticut School of Medicine

9:49-9:59AM - Adult Brain Tumors as a Paradigm for Studying Tumor Evolution
Roel Verhaak, Ph.D., The Jackson Laboratory for Genomic Medicine

10:02-10:12AM - Genomic and Epigenomic Signatures of Sociopolitical Histories in the Americas
Deborah Bolnick, Ph.D., University of Connecticut

10:15-10:30AM - BREAK

10:30-10:40AM - Integrative Genomics and Clinical Data Analysis for Precision Medicine
Zeeshan Ahmed, Ph.D., University of Connecticut School of Medicine

10:43-10:53AM - Structural Variation and Homologous Sequences
Christine Beck, Ph.D., University of Connecticut School of Medicine and The Jackson Laboratory for Genomic Medicine

10:56-11:06AM - Triangulating the Genetic Basis of Recently Evolved Gain-of-Immunity of Stickleback Fish Against Their Cestode Parasite
Daniel Bolnick, Ph.D., University of Connecticut

11:09-11:19AM - Clinical Genomics at an Academic Center
Honey Reddi, Ph.D., The Jackson Laboratory for Genomic Medicine

11:22-11:32AM - Myostatin: a Molecular Rheostat for Muscle Mass
Se-Jin Lee, M.D., Ph.D., University of Connecticut School of Medicine and The Jackson Laboratory for Genomic Medicine

11:35-12:30PM - Lunch

12:35-12:50PM - Center for Genome Innovation
Bo Reese, Ph.D. University of Connecticut

12:50-1:05PM - Computational Biology Core
Jill Wegrzyn, Ph.D., University of Connecticut

1:05-1:20PM - Single Cell Genomics Center
Paul Robson, Ph.D., The Jackson Laboratory for Genomic Medicine

1:25-1:45PM - High Throughput Methods for Understanding Impacts of Variants on Enhancer Function
Justin Cotney, Ph.D., University of Connecticut School of Medicine

1:47-2:07PM - Measuring the Kinetics of Co-Transcriptional Splicing with Nascent RNA Sequencing
Leighton Core, Ph.D., University of Connecticut

2:09-2:29PM - Tackling the Repertoire of Human Isoforms Through Long-Read Sequencing
Jacques Blanchereau, Ph.D., The Jackson Laboratory for Genomic Medicine

2:30PM - Closing Remarks
Rachel O’Neill, Ph.D., University of Connecticut

2:45PM - Conference adjourns
Abstracts:

Challenges and opportunities in metagenomic and metatranscriptomic profiling of mouse gut microbiota

Mark D. Adams, The Jackson Laboratory

The laboratory mouse increasingly plays a central role in demonstrating causality and dissecting the mechanisms by which microbes impact host phenotypes. The reference databases for mouse microbiome profiling are much less well developed than those for human-associated microbial environments: generally less than 25% of metagenomic reads can be mapped to known reference genomes. We are working to enhance both 16S rRNA and metagenome resources to assist in characterizing mouse microbiomes using diverse mouse models including diversity outbred (DO) mice and strains from the Knockout Mouse Project (KOMP). One system has been explored in depth. A newly identified mouse mutant (HLB444) is resistant to obesity on a high-fat (HF) diet and has elevated plasma triglycerides. We profiled the microbiome of HLB444 & wild-type control animals on chow diet and after shift to HF diet. 16S rRNA V1-V3 was sequenced and whole metagenome shotgun sequence (mWGS) data and metatranscriptome data were obtained. Assembled mWGS and metatranscriptome data were integrated to define differentially expressed genes. Control and mutant animals showed marked differences in microbial community composition on chow. Following HF exposure, both genotypes demonstrated rapid alterations in community structure. Gut microbial communities in HLB444 and B6 animals differed in their response to HF diet, with B6 exhibiting a loss of Anaeroplasma and HLB444 exhibiting an increase in Akkermansia. The ratio of Bacteroidetes to Firmicutes declined in both genotypes, with a greater difference in HLB444 animals. Fewer than half of predicted coding regions were detected as expressed and these provided a more informative view of functional differences between samples. Genetic and environmental perturbations can shape the gut microbial community of both humans and mice. Analysis of the differential response of HLB444 to HF diet provides insight into the role of the microbiome in adapting to dietary change and serves as a foundation for enhancing 16S rRNA and reference genome sequences.

Genetics in weight loss and dietary intake

Jeanne McCaffery, University of Connecticut, Storrs

Obesity is a critical public health problem. Over one third of U.S. adults are obese and suffer increased risk for type 2 diabetes, cardiovascular disease and certain types of cancer. Genome-wide association study has discovered numerous genetic loci predictive of obesity. In this presentation, I will highlight my research examining whether genetic loci that increase risk for obesity inhibit individuals from losing weight with effective weight loss intervention. I will also present my research demonstrating that genetic loci associated with obesity predict obesogenic diet patterns. I will conclude by reviewing future directions in this research.

Application of Targeted Screening Approaches to Advance Understanding of RNAbp Roles in Endothelial Regulation of Inflammation

Patrick Murphy, University of Connecticut School of Medicine

We recently identified a broad alternative splicing response in the endothelium in response to innate immune cell recruitment (eLife, 2018). By excision of alternative exons in Fn1, we have shown that components of this splicing response can regulate inflammatory induced changes in extracellular matrix composition and immune cell function. We have found that these splicing changes are protective against intimal rupture under disturbed flow conditions found in atherosclerosis and aneurysm (ATVB, 2014). Thus, we hypothesize that the RNAbp splice factors regulating these and the other splicing changes we have observed play an important role in vascular inflammation. But bioinformatic analysis suggests the involvement of specific RNAbp splice factors, their roles must be functionally defined. We have established an in vitro system which replicates in vivo splicing and inflammatory changes, providing a platform for CRISPR mediated screens of RNAbp function in both. By developing single-cell readouts of RNA splicing and key inflammatory responses, we have been able to use targeted FACs-based CRISPR screens to define the role of specific splice factors in both.

Adult brain tumors as a paradigm for studying tumor evolution

Roel Verhaak, The Jackson Laboratory

Adult brain tumors represent a heterogeneous group of diseases. Among these, gliomas are particularly notorious as they often are diagnosed at the prime of life but have minimal treatment options. We study adult gliomas using genomics and computational approaches, with the goal of understanding therapy resistance and improving patient outcomes.
Genomic and Epigenomic Signatures of Sociopolitical Histories in the Americas

Deborah Bolnick, University of Connecticut, Storrs

While biologists have long sought to understand how genetic factors and molecular processes shape human development, phenotypes, and behavior, less attention has been given to the ways that human behavior, experience, and history shape the genome itself. In this presentation, I will consider the genomic and epigenomic impacts of both large-scale sociopolitical events and individual life experiences, drawing on studies of DNA from both ancient and contemporary Indigenous peoples in the Americas.

Integrative Genomics and Clinical Data Analysis for Precision Medicine

Zeeshan Ahmed, University of Connecticut School of Medicine

Innovative platforms are necessary to improve the quality and transition of healthcare for investigating heterogeneous clinical data to obtain actionable care gap-based information about patients for early detection and prevention of constitutional disorders and cancer, and developing efficient communication and coordination across healthcare units and scientific labs. This talk introduces a new platform i.e., PROMIS-Med, presented by the Ahmed lab at the Genetics and Genome Sciences, UConn Health. PROMIS-Med aims to be an advanced academic solution with effective, integrative and analytic access to clinical, epidemiological, metabolomics and genomics data of huge volume, velocity, variety, and veracity, and with the potential to revolutionize the field of medicine with best strategies to diagnose and treat patients, and developing better understanding of biology.

Structural variation and homologous sequences

Christine Beck, The University of Connecticut School of Medicine and The Jackson Laboratory for Genomic Medicine

Approximately 50% of the genome is comprised of mobile elements, and these sequences can lead to genomic instability through a variety of mechanisms. I am specifically focused on how transposable elements underlie breakpoints of structural variation, how common these events are, and what other genomic sequence features are associated with this form of instability.

Triangulating the genetic basis of recently evolved gain-of-immunity of stickleback fish against their cestode parasite

Daniel Bolnick, University of Connecticut, Storrs

Parasite communities vary dramatically a landscape. This spatial variation in infection can drive host evolution, but may also be a result of that evolution. We recently showed that some populations of threespine stickleback (a small fish) have evolved dramatic new immunity to their native cestode parasite. Some stickleback populations can suppress tapeworm growth by orders of magnitude, and in doing so can frequently eliminate the parasite. However, this immunity comes with a substantial cost in the form of a fibrosis immunopathology. We are using a combination of high throughput transcriptomics, population genomics, genome-wide association mapping, and quantitative trait locus mapping, to pinpoint the immunogenetic basis of this recently evolved immunity and its associated pathology.

Clinical genomics at an academic center

Honey Reddi, The Jackson Laboratory

Genomics for precision medicine is standard of care, particularly in Oncology. We will look at the menu of assays the Jackson laboratory currently has and its efforts to address the unmet needs of the patient.

Myostatin: a molecular rheostat for muscle mass

Se-in Lee, University of Connecticut School of Medicine and The Jackson Laboratory for Genomic Medicine

The main focus of our research is to understand the control of muscle growth by myostatin. Myostatin is a secreted signaling molecule that we discovered many years ago in a screen that we carried out to identify new members of the transforming growth factor-ß superfamily. We showed that mice lacking myostatin exhibit dramatic increases in muscle mass as a result of increased numbers of muscle fibers and increased myofiber sizes. Using biochemical approaches, we and others have identified key regulatory and signaling components for myostatin. Much of our work has focused on using genetic approaches in mice to investigate the roles of these components in vivo. We are currently analyzing mouse lines that we have generated in which we have introduced both deletion and floxed alleles for many of these regulatory components. We are also interested in understanding the roles of this regulatory system in tissue aging, particularly with respect to metabolic dysfunction and heart disease.
High throughput methods for understanding impacts of variants on enhancer function

Justin Cotney, University of Connecticut School of Medicine

Chromatin state profiling has revealed hundreds of thousands of tissue-specific regulatory regions across the human genome. Variants associated with disease states of tissues are enriched in cognate tissue-specific enhancers. For example, we have recently shown that variants associated with risk for nonsyndromic cleft lip with or without cleft palate are systematic enriched in enhancers active during early craniofacial development. It is unclear however what genes these regulatory regions directly control and what effect variants have on their activity. We are currently developing and employing methods to systematically test large numbers of variants in thousands of regulatory regions and measure their effects on enhancer activity and target gene expression.

Measuring the kinetics of co-transcriptional splicing with nascent RNA sequencing

Geno Villafano and Leighton Core, University of Connecticut

Regulation of RNA splicing is critical for proper gene expression levels and generation of transcript diversity, and its misregulation is the basis for numerous diseases. It is now well established that a majority of RNA splicing takes place as the RNA is still being transcribed by RNA polymerase II. Consequentially, regulation of transcription and splicing are intertwined presenting a novel framework for the study of disease-associated mutations in either process. However, connecting splicing rate and with transcription regulation is difficult due to numerous technical challenges. In addition, splicing efficiency is difficult to measure since mis-spliced transcripts are often undetectable due to their rapid degradation. Here, we address these issues by combining precision run-on sequencing (PRO-seq) with fulllength RNA sequencing on oxford nanopore’s technology. The adaptations allow us to map the position of RNA polymerase II when co-transcriptional splicing occurs. Our approach achieves near base pair resolution and initial results from Drosophila S2 cells suggest that splicing occurs within seconds of the downstream splice sites becoming accessible to the spliceosome.

Tackling the Repertoire of Human Isoforms Through Long-Read Sequencing

Jacques Banchereau, The Jackson Laboratory for Genomic Medicine


Isoforms are alternatively spliced forms of mRNA transcribed from the same gene that differ in the exons included in the mRNA transcript. This greatly increases the diversity of proteins translated from a single gene, and it is estimated that the ~23,000 human genes might generate >100,000 isoforms. Until now, tools to study isoforms have been limiting and are inadequate to capture complex splicing events involving non-adjacent exons. To understand the complexity of the human splicing isoform repertoire, we used a combination of short-read (Illumina RNA-seq) and long-read RNA sequencing (PacBio) technologies. To analyze the very large datasets, we established a suite of software assembled from different sources including our own scripts. We will present examples of novel isoforms identified in human blood mononuclear cells as well as human tumors. These novel entities might represent biomarkers of disease activity or targets for therapeutic intervention. With regard to cancer, we will discuss the example of “shared neoantigens” that can be used to vaccinate cancer patients receiving checkpoint inhibitors and cell surface cancer-specific isoforms that can be used to generate therapeutic monoclonal antibodies.

Funding: The Jackson Laboratory; The Parker Institute for Cancer Immunotherapy; NIAMS P50 AR070594, NIAID U01 AI124297, NIA R01 AG052608.