Agenda:

Much appreciation for your patience if the timing on our agenda becomes slightly off.

11:00AM	Welcome **Rachel O'Neill, Ph.D., Director, Institute for Systems Genomics, University of Connecticut**
11:05	Introductory Remarks **Edison Liu, M.D., President and CEO of The Jackson Laboratory**
11:10	*From genomics to therapeutics: single-cell dissection and manipulation of disease circuitry* **Manolis Kellis, Ph.D.** **Computer Science and Artificial Intelligence Lab, Massachusetts Institute of Technology** **Member, Broad Institute of MIT and Harvard**
12:00PM	Poster Session Set 1: 12:00-12:30 featuring Agarwal, Chung, Cobo-Simon, Desiato, Drennan, Gorka, Grady, Hoyt, Kim Set 2: 12:30-1:00 featuring Marazzi, Massey/Salles/Senechal, Neitzey, Pan, Weiner, Wentworth Winchester, Wojenski, Yankee, Zhu
1:00	Computational Biology Core **Jill Wegrzyn, Ph.D., University of Connecticut**
1:03	Center for Genome Innovation **Bo Reese, Ph.D. University of Connecticut**
1:06	Microbial Analysis, Resources and Services Facility **Kendra Maas, Ph.D., University of Connecticut**
1:09	Single Cell Genomics Facility **Paul Robson, Ph.D., The Jackson Laboratory for Genomic Medicine**
1:12	Concurrent Breakout Sessions with ISG Core Directors and Vendors **Featuring Oxford Nanopore Technologies and Geneious**
1:45	*Alternative RNA Splicing Defects in Cancer: Molecular and Therapeutic Insights from Model Systems* **Olga Anczuków, Ph.D., The Jackson Laboratory for Genomic Medicine**
1:58	*Functional regulation and diploid genome architecture in multicellular organisms* **Jelena Erceg Ph.D., University of Connecticut**
2:11	*Targeting $p21^{Cip1}$-Highly-Expressing Cells in Adipose Tissue Alleviates Insulin Resistance in Obesity* **Ming Xu Ph.D., University of Connecticut School of Medicine**
2:24	*Understanding Horizontal Gene Transfer: Units of Transfer and Modes of Integration* **Mukul Bansal Ph.D., University of Connecticut**
2:37	*Effects of urbanization on host resistance to invasive parasites in the Galapagos Islands* **Sarah Knutie, Ph.D., University of Connecticut**
2:50	Closing Remarks **Brenton Graveley, Ph.D., Associate Director, Institute for Systems Genomics,** **University of Connecticut School of Medicine**
3:00	Virtual Happy Hour

Speaker Abstracts:

Manolis Kellis, Ph.D.

Professor, Computer Science and Artificial Intelligence Lab
Massachusetts Institute of Technology
Member, Broad Institute of MIT and Harvard

From genomics to therapeutics: single-cell dissection and manipulation of disease circuitry

Disease-associated nucleotides lie primarily in non-coding regions, increasing the urgency of understanding how gene-regulatory circuitry impacts human disease. To address this challenge, we generate transcriptional and epigenomic maps of 823 human tissues, 1500 individuals, and 7.5 million single cells. We link variants to target genes, upstream regulators, cell types of action, and perturbed pathways, and predict causal genes and regions to provide unbiased views of disease mechanisms, sometimes re-shaping our understanding. We find that Alzheimer's variants act primarily through immune processes, rather than neuronal processes, and the strongest genetic association with obesity acts via energy storage/dissipation rather than appetite/exercise decisions. We combine single-cell profiles, tissue-level variation, and genetic variation across healthy and diseased individuals to deconvolve bulk profiles into single-cell profiles, to recognize changes in cell type proportion associated with disease and aging, to partition genetic effects into the individual cell types where they act, and to recognize cell-type-specific and disease-associated somatic mutations in exonic regions indicative of mosaicism. We expand these methods to electronic health records to recognize meta-phenotypes associated with combinations of clinical notes, prescriptions, lab tests, and billing codes, to impute missing phenotypes in sparse medical records, and to recognize the molecular pathways underlying complex meta-phenotypes in genotyped individuals by integration of molecular phenotypes imputed in disease-relevant cell types. Lastly, we develop programmable and modular technologies for manipulating these pathways by high-throughput reporter assays, genome editing, and gene targeting in human cells and mice, demonstrating tissue-autonomous therapeutic avenues in Alzheimer's, obesity, and cancer. These results provide a roadmap for translating genetic findings into mechanistic insights and ultimately new therapeutic avenues for complex disease and cancer.

Olga Anczuków, Ph.D.

Assistant Professor
The Jackson Laboratory for Genomic Medicine

Alternative RNA Splicing Defects in Cancer: Molecular and Therapeutic Insights From ModelSystems

Alternative RNA splicing is a key step in gene expression regulation and a source of transcriptomic and functional diversity that allows to generate multiple RNA isoforms from the same gene. Proper regulation of alternative splicing is key for normal development, and dysregulation of splicing-factor proteins is at the center of human diseases including cancer. Human tumors often exhibit alterations in splicing factors; however the functional significance of these alterations, their molecular drivers, and their contribution to disease pathogenesis are only beginning to be unraveled.

Work from our lab focuses on SR proteins, a family of 14 essential splicing factors, which are often upregulated in solid tumors, including in breast. We demonstrated that only specific splicing factors from the SR protein family promote mammary cell transformation and/or metastasis in *in vitro* and *in vivo* breast cancer models. We further investigate the transcriptional and post-transcriptional regulatory mechanisms that control splicing-factor levels in normal mammary cells and their misregulation in cancer cells. We demonstrate the MYC oncogene directly regulates a network of splicing factors that are co-expressed in tumors and act together to regulate their downstream targets and promote cell invasion. In parallel, our work reveals the role of non-coding 'poison exon' in regulating SR proteins levels during cell differentiation and in tumors. We uncover an extensive cross-regulatory network used by the SR protein family to control their expression. Finally, we develop splice-switching antisense oligonucleotides to reverse the increased skipping of TRA2β poison exon detected in breast tumors, leading to increased cell death and decreased cell migration in breast cancer models.

In summary, our work provides new insights into the regulatory mechanisms of SR proteins and identifies novel oncogenic spliced isoforms that represent potential biomarkers and targets for therapeutics development.

Mukul Bansal Ph.D.

Associate Professor
Department of Computer Science & Engineering
University of Connecticut

Understanding Horizontal Gene Transfer: Units of Transfer and Modes of Integration

Understanding the evolutionary processes that have created and shaped all life on Earth is a fundamental problem in biology. Over the last decade or so, several highly effective computational methods have been developed for studying gene family evolution and horizontal gene transfer (HGT) in microbes. This is the result of many algorithmic and methodological advances, by us and others, that have had significant impact on the applicability and accuracy of these computational techniques. In this talk, we will discuss how these advances have recently been leveraged to better understand two key properties of HGT events: their units of transfer, i.e., the "size" of individual transfer events, and their modes of integration, i.e., whether the transfer is "additive" or "replacing".

Jelena Erceg, Ph.D.

Assistant Professor
Department of Molecular and Cell Biology
Institute for Systems Genomics
University of Connecticut

Functional regulation and diploid genome architecture in multicellular organisms

Multicellular organisms are composed of diverse cell types that originate from a single cell. However, much less is known how gene regulation and unique architecture of diploid genome contribute to achieve this diversity. Using haplotype-resolved Hi-C and Oligopaints-based imaging, our studies reveal how two haploid genomes organize themselves and contact each other within the confines of a diploid nucleus. These haplotype-resolved 3D structures display global connections with paradigms governing gene regulation during development. Finally, we demonstrate flexibility or stability of structural hallmarks within genome organization in evolution, as measured by ultraconservation of DNA sequence.

Sarah Knutie, Ph.D.

Assistant Professor
Department of Ecology and Evolutionary Biology
University of Connecticut

Effects of urbanization on host resistance to invasive parasites in the Galapagos Islands

Human population size is increasing exponentially and, in turn, the urban environment is one of the few ecosystems that is rapidly expanding. A recent example of urbanization is in the Galapagos Islands, which is home to the iconic and endemic Darwin's finches. The Galapagos Islands currently hosts 225,000 tourists each year and is home to over 21,300 permanent residents. Consequently, humans have altered the natural habitat and introduced parasites to the Islands, such as the avian vampire fly (*Philornis downsi*), which causes up to 100% mortality in nestling finches. However, our recent experimental work shows that small ground finches (*Geospiza fuliginosa*; a species of Darwin's finch) in urban areas are less affected by the parasite compared to finches in non-urban areas because urban birds have fewer parasites than non-urban birds. Furthermore, our work suggests that urban birds are more resistant to the parasite than non-urban birds. The mechanisms of host resistance, as well as the potential factors promoting this defense in urban areas, will be discussed.

Ming Xu, Ph.D.

Assistant Professor
UConn Center on Aging
Department of Genetics and Genome Sciences
University of Connecticut School of Medicine

Targeting *p21*^{Cip1}-Highly-Expressing Cells in Adipose Tissue Alleviates Insulin Resistance in Obesity

Insulin resistance is a common pathological state strongly associated with obesity, representing a major risk factor for

type 2 diabetes (T2D) and its complications. Limited mechanism-based strategies exist to alleviate insulin resistance. Here, using single-cell transcriptomics, we identify a small, critically important, but previously unexamined cell population, p21Cip1-highly-expressing (p21high) cells, which accumulate in adipose tissue in obese mice. By leveraging a new p21-Cre mouse model, we demonstrate that intermittent clearance of p21high cells can both prevent and alleviate insulin resistance in obese mice. Exclusive inactivation of NF-κB pathway within p21high cells attenuates insulin resistance. Moreover, adipose tissue transplantation experiments establish that p21high cells within visceral adipose tissue are sufficient to cause insulin resistance in vivo. Importantly, a senolytic cocktail, dasatinib plus quercetin, reduces p21high cells in adipose tissue explants isolated from obese human subjects, and mitigates insulin resistance following transplantation into immuno-deficient recipient mice. Our findings lay the foundation for pursuing p21high cells as a new therapeutic target for alleviating insulin resistance, paving the way for future clinical trials of dasatinib plus quercetin in T2D.