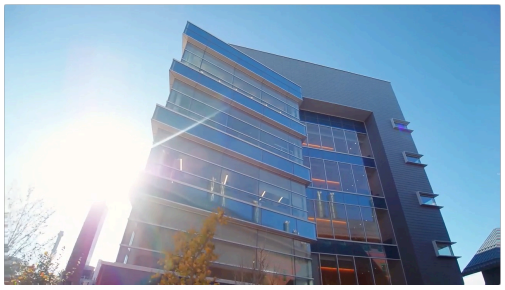
Institute for Systems Genomics Newsletter

July 2018

Engineering and Science Building



Click ESB photo to active video

On Monday, June 11, 2018, UConn held a ribbon-cutting ceremony to celebrate the opening of the Engineering and Science Building. The ISG occupies two floors of this state-of-the-art building which was built as part of the state's Next Generation Connecticut Initiative. The event included Governor Dannel Malloy, UConn President Susan Herbst, legislators, industry partners, faculty, students, and researchers.

Institute for Systems Genomics Executive Committee

An ISG Executive Committee has been established to assess the goals and mission statement of the ISG, review membership, guide decisions in future programs and support services, review reports from cores, centers and programs within the ISG, and target new initiatives and collaborative/consortium awards. The ISG Executive Committee includes:

Rachel O'Neill, Director, Institute for Systems Genomics
Brenton Graveley, Associate Director, Institute for Systems Genomics
Gerry Altmann, College of Liberal Arts and Sciences
Robert Bird. School of Business
Michael Glasgow, Office of the Vice President for Research
Charles Lee, The Jackson Laboratory for Genomic Medicine
Jeanne McCaffery, College of Agriculture, Health & Natural Resources
Juan Salazar, Connecticut Children's Medical Center
Jeffrey Shoulson, Office of the Provost
Mei Wei, School of Engineering
Sandra Weller, School of Medicine
Louis Bach *(ad hoc),* Foundation
Andrea Keilty *(ad hoc),* Governmental Relations
Joann Lombardo *(ad hoc),* Governmental Relations

A ribbon-cutting ceremony featuring President Susan Herbst and Governor Dannel Malloy was held for the Engineering & Science Building in Storrs. (Peter Morenus/UConn Photo)

The PromethION has arrived in the Center for Genome Innovation

PromethION Nanopore

PromethION offers the same real-time, long-read, direct DNA and RNA sequencing technology, and is designed to run up to 48 flow cells at any time.

UConn and The Jackson Laboratory for Genomic Medicine submit a T32 Training Grant

In May 2018, a T32 training grant entitled "The UConn/JAX-GM Training Program in Genomic Science" was submitted by **Dr. Brenton Graveley** and **Dr. Charles Lee** to the National Human Genome Research Institute to support the training of 8 predoctoral and 2 postdoctoral trainees in the genomic sciences. The goal is to provide pre- and postdoctoral trainees with a strong foundation in computational skills and research design to answer emerging questions in biomedical science made accessible by high-throughput sequencing techniques. Trainees will benefit from the established cross-institutional collaborations among faculty trainers, including cross-institutional co-mentorship opportunities, and a strong team science environment. This proposal strengthens the relationship between JAX-GM and UConn.

Upcoming Events

Computational Biology Core

RNA-Seq: Experimental Design and Analysis (Bioinformatics)

Dates/Time: **July 26-27 2018, 9:00-5:00 pm**
Location: **Engineering and Science Building, Room 304, Storrs Campus**
Enroll: http://bioinformatics.uconn.edu/cbc-workshop/
Cost: **$600**

CBC Workshops are open to advanced undergraduates, graduate students, postdocs, and faculty. Each class enrolls a max 10 students and provides hands-on training and background for genomics data analysis. Two instructors are available to assist participants. All materials, including sample and processed data files, are available after the course ends.

Course material will introduce students to HPC, command-line bioinformatics software, and standard informatics pipelines for processing RNA-Seq data. We will cover the basics for both model (reference genome) and non-model (*de novo* transcriptome) approaches. Previous experience with HPC and/or programming are not required.

ISG Spotlight

Joint JAX-UConn Assistant Professor, **J. Travis Hinson**, was awarded his first R01 from the National Institutes of Health/National Heart, Lung, and Blood Institute for his project entitled: "Comprehensive Analysis of Allelic, Cellular and Molecular Heterogeneity in Human 3-Dimensional Cardiac Microtissue". This is a 4-year grant for $2.1 million.

J. Travis Hinson, M.D.

Hypertrophic cardiomyopathy (HCM) patients are at risk for sudden cardiac death and progressive heart failure (HF), and there are no effective therapeutics, due in part to our limited genetic understanding of HCM pathogenesis. With critical gaps in our current knowledge of the molecular mechanisms that link specific mutations in the beta myosin heavy chain gene (MYH7) to pathological thickening of the heart muscle that is associated with HCM, Dr. Hinson's research will have the potential to reveal patient-specific insights into HCM pathogenesis and identify novel therapeutic targets. The goal of the project is to determine how MYH7 variants cause heart failure by utilizing cardiac microtissues derived from human induced pluripotent stem cells.

Illustration by UConn undergrad, Hayley Joyal

Dr. Brenton Graveley and Dr. Sandra Garrett collaborated with Dr. Michael Terns and Dr. Masami Shiimori at the University of Georgia to study the CRISPR-Cas system, a defense mechanism that has evolved in bacteria and archaea that these single celled organisms use to ward off attacks from viruses and other invaders. The researchers sequenced millions of genomes to learn more about biological mechanisms involved in CRISPR-Cas. "In this project, we were able to determine how the bacterial immune system creates a molecular memory to remove harmful viral DNA sequences and how this is passed down to the bacterial progeny," said Graveley.

This long-standing collaboration between the Graveley and Terns labs has led to numerous publications, and funding from the National Institutes of Health. Their latest research was published in the journal Molecular Cell, and the artwork depicting CRISPR adaptation was created by UConn undergraduate Hayley Joyal and featured on the journal's cover (Link to publication).

ISG director, **Rachel O'Neill**, is part of an international team (led by Rebecca Johnson) that sequenced the first full koala genome. The study was published online in *Nature Genetics* on July 2, 2018. These data form the most complete marsupial genome recorded to date, provide insights into the koala's unique biology, and may aid in the treatment of disease and help inform conservation efforts. The team assembled a high-quality koala genome using long-read sequencing technology and optical mapping.

Koalas are threatened by increasing habitat loss, fragmentation of their population and disease susceptibility. These findings allow the reconstruction of koala demographic histories and the assessment of current population diversity—making the genome a rich resource for shaping future conservation initiatives.

Center for Genome Innovation (CGI)

Do you know the genome lurking in your cell lines? What is a faster way to confirm genome integrity than a karyotype? What single test provides both high resolution copy number and SNP analysis? The CGI and the Chromosome Core now offer services on the NEW Illumina Infinium CytoSNP 850K bead array!

Cells in culture can change over time due to experimental manipulations, off-target editing effects, or, most commonly just by random, often large-scale, alterations that occur during cell-line maintenance and expansion. For example, genome, proteome and phenotypic heterogeneity and instability was recently reported for 14 stock HeLa cell aliquots from 13 different laboratories across the globe (http://dx.doi.org/10.1101/307421).

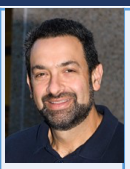
Center for Genome Innovation (CGI) - continued

The degree of variability that was uncovered for HeLa, the most extensively studied and widely used human cell line, underscores the need to ensure genomic stability in all human tissue cell lines and to appropriately report instability in lines used for ongoing studies. To date, we have reported expected normal, expected abnormal, and unexpected abnormal data for iPSCs and CRISPR-manipulated iPSCs from multiple principal investigators, helping them discern which lines are best to propogate and study.

Using the Illumina Infinium CytoSNP 850K bead array, the CGI can easily characterize your cell lines by assaying unbalanced chromosomal abnormalities, copy number variants (CNVs), loss of heterozygosity (LOH) and single nucleotide polymorphisms (SNPs). Having confidence in what you are working with will not only give you piece of mind, it could save you from months of agonizing (and costly) troubleshooting! This type of data also meets the biological validation requirements from various funding agencies (NIH, NSF, etc) and journals (*Cell* Press, *Nature*, Springer, etc).

The cost per sample (with a minimum of 4 samples needed for processing) is $425. The cost per sample decreases with increasing sample numbers; 5-8 samples = $350/sample and 9-16+ samples = $300/sample. Costs include sample QC, labor and a customized report. For more information about this service, please contact either Dr. Judy Brown (judy.brown@uconn.edu) or Dr. Bo Reese (bo.reese@uconn.edu).

ISG Faculty – New Awards



Adam Adler received a 2-year, $439K, award from the National Institutes of Health/National Institute of Allergy and Infectious Disease for his project entitled: "Test if Anti-tumor T Cells use a Putative Super Enhancer in the IL1R2-IL1R1 Intergeneric Region to Form "Innate-Like" Responses to Cytokines". The goals of this project are to: 1) characterize IL-2-associated DNA loops extending from the *Il1rl2-Il1rl1* intergenic STAT5 binding sites using 4C chromatin conformation capture analysis, 2) generate mice with edited STAT5 binding sites in the putative *Il1rl2-Il1rl1* super-enhancer, and 3) assess the role of the putative *Il1rl2-Il1rl1* super-enhancer in effector T cell function and therapeutic antitumor immunity.

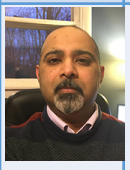
Congratulations to **Floris Barthel,** JAX postdoctoral associate, on his 5-year Pathway to Independence Award from the National Institutes of Health/National Cancer Institute for his project entitled: "Genetic and Epigenetic Strategies for the Acquisition of Telomere Maintenance in Human Cancer Cells". This award will support his work to better understand the critical role of the protein telomerase in cancer development and enable the development of new cancer treatment strategies that reduce or eliminate telomerase activity without affecting non-cancer cells.

JAX assistant professor**, Albert Cheng,** received a 5-year, $3.2 million award from the National Human Genome Research Institute for his project entitled: "Modular Platforms for Combinatorial Epigenome Manipulation". The goal of the project is to develop state-of-the-art tools to more precisely manipulate epigenetic regulation.

JAX associate professor, **Jeffrey Chuang**, has been awarded a 5-year, $2.65 million grant from the National Institutes of Health/National Cancer Institute for his project entitled: "Quantitative Computational Methods to Accurately Measure Tumor Heterogeneity in Solid Tumors to Inform Development of Evolution-Based Treatment Strategies".

Congratulations to **Brenton Graveley**, whose ENCODE resubmission was successful, with a $9 million, 4-year award from the National Human Genome Research Institute. This grant will support his work mapping the sites for all human RNA binding proteins.

UConn Health endocrinologist, **Marja Hurley**, recently received a $1.75M grant from the National Institutes of Health for her project entitled: "FGF2 Isoforms in Bone and Phosphate Homeostasis". The goal is to utilize transgenic mouse models developed in the Hurley lab that phenocopy human X-linked hypophosphatemia (XLH) to elucidate the molecular mechanism(s) of the osteoarthropathy associated with XLH for which there is no effective therapy.



Rahul Kanadia recently received a 5-year, $1.8 million award from the National Institutes of Health/National Institute of Neurological Disorders and Stroke for his project entitled: "Understanding the Role of Minor Intron Spliceosome in Cortical Development". Dr. Kanadia's lab is exploring how splicing of a sub-type of introns regulate gene expression during normal cortical development. Importantly, we want to understand how failure to process these introns results in the disease microcephalic osteodysplastic primordial dwarfism type 1 (MOPD1).

UConn Health/JAX Professor, **Reinhard Laubenbacher**, recently received two National Institutes of Health grants (totaling over $5.2 million). One of the grants (4-year award) is entitled: ""Control of Heterogeneous Microbial Communities Using Model-Based Multi-Objective Optimization", and is in collaboration with Pedro Mendes and Anna Dongari-Bagtzoglou. The second grant, a 5-year award, is for his research project entitled: "Multiscale Modeling of the Battle over Iron in Invasive Lung Infection". Additionally, Dr. Laubenbacher received support from the Mayday Fund to form the Connecticut Pain Consortium.

ISG Faculty – New Awards (continued)

Professor **James Li** received a 5-year, $2 million, award from the National Institutes of Health for his project entitled: "Molecular Regulation of Lineage Specification of the Mouse Cerebellum". The goal of this project is to use single-cell RNA sequencing and genetic studies to determine how various cerebellar neuronal and glial cells are generated, and how these cells are assembled into functional cerebellar circuits.

NIH awarded a 5-year, $6.5 million grant to an international team led by Herbert Sauro at the University of Washington and **Ion Moraru** to establish a new "Center for Reproducible Biomedical Modeling". Center investigators, will develop new tools and technologies to accelerate the creation and use of predictive models that can guide medicine and bioengineering (link to Center website).

Rachel O'Neill received an award from the Connecticut Bioscience Innovation Fund for the UConn-Wesleyan Stem Cell Core.

Stefan Pinter received a 4-year, $2 million, award from the National Institutes of Health/National Heart, Lung and Blood Institute for his project entitled: "Contributions of Sex Chromosomal Gene Homologues to X Monosomy". This research project grant investigates gene pairs that are common to X and Y chromosomes, to understand how they contribute to phenotypes of X monosomy. In Turner syndrome, these include high rates of spontaneous termination and aortic aneurysms. The lab aims to model aortic defects using *in vitro*-derived smooth muscle cells (SMCs) from isogenic iPSCs that differ only in the presence of the second sex chromosome.

JAX assistant professor**, Michael Stitzel** received an American Diabetes 2018 Pathway to Stop Diabetes Accelerator Award for his project entitled: "Deciphering longitudinal cell type-specific defects in diabetes pathogenesis". This 5-year, $1.6 million, project seeks to build and apply innovative genomic tools and technologies to identify, and ultimately manipulate, cell type-specific molecular signatures of human pancreatic islet dysfunction in type 2 diabetes. He anticipate that by investigating all islet cell types, including those that have been understudied in favor of the insulin-producing beta cells, he will uncover important new genes and pathways modulating islet cell identity, function, and resilience that can be exploited to monitor, prevent, and treat islet dysfunction and type 2 diabetes.

Congratulations to JAX assistant professor, **Adam Williams,** on his two National Institutes of Health/National Institute of Allergy and Infectious Diseases R21 awards (totaling over $1 million). The goals of these projects are to: 1) to identify long noncoding RNAs (lncRNAs) that play a role in the antiviral response of human primary bronchial epithelial cells (BECs) to rhinovirus infection; 2) to test the hypothesis that the lncRNA Morrbid is required for the survival of activated DCs to initiate robust T cell-mediated immune responses.

ISG Accomplishments, Service, and Presentations

Adam Adler NIH study sections. Chair, NCI Program Project I (P01) Review Committee, ZCA1 RPRB-N (M2), NIH (2018). Ad hoc member, "Transition to Independence" NCI study section, NIH

Judith Blake serves on NIH/NHGRI GNOM-G panel as a permanent member

Gregory Carter - NIH study sections: Cellular and Molecular Biology of Neurodegeneration Study Section; Fellowship: Genes, Genomes, and Genetics [F08] Study Section

Marja Hurley was appointed Translational Chair of the Planning Committee for the 2018 American Society for Bone and Mineral Research Annual Meeting to be held in Montreal, Canada. Dr. Hurley was also invited to speak for the 2018 Avioli Musculoskeletal Research Seminar Series at Washington University in St, Louis, MO. The title of her talk is "High Molecular Weight Isoforms of Fibroblast growth factor 2, New Players in Osteoarthropathy"

Leslie Loew served on the NIH Cancer Systems Biology Study Section. Dr. Loew also received the Biophysical Society Distinguished Service Award at the Annual Meeting in February in San Francisco.

Akiko Nishiyama was elected to the Connecticut Academy of Science and Engineering in 2018.

Joel Pachter served on NIH study section Study Section ZRG1 MDCN M91 (Special Emphasis Panel, The Blood-Brain Barrier, Neurovascular System and CNS Therapeutics). Selected as permanent member to NIH Study Section BINP (Brain Injury and Neurovascular Pathology)

Blanka Rogina participated in a review panel for the NIGMS Postdoctoral Research Associate Fellowships, Bethesda, MD, March 28.

Roel Verhaak served as an ad hoc member of the NIH/NCI Cancer Genetics (CG) study section, as well as the Clinical Neuroimmunology and Brain Tumors Study Section [CNBT].

Andrew Wiemer received the Young Investigator Award from the American Chemical Society, and presented a talk on this research entitled "Immune modulation by butyrophilin ligands and their prodrugs" at their national meeting in New Orleans on March 19, 2018.

Publications

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Congratulations to Steve King

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