

4th Annual Symposium on Multiscale Cell Fate Research



The Beckman Center of the National Academies of Sciences and Engineering

SPEAKERS



GREG FOREST

University of North Carolina at Chapel Hill



IGOR ADAMEYKO Medical University of Vienna



MANOLIS KELLIS



MAKSIM PLIKUS University of California, Irvine



SARAH MILLAR Icahn School of Medicine at Mount Sinai



FEI CHEN Broad Institute of MIT and Harvard



JOSÉ ONUCHIC Rice University



TIM DOWNING University of California, Irvine



APRIL PYLE University of California, Los Angeles



STACY FINLEY University of Southern California



STANISLAV SHVARTSMAN Princeton University

EVENT PROGRAM

Thursday, October 28

07:30 am - 08:25 am	BREAKFAST
08:25 am - 08:30 am	OPENING ADDRESS
08:30 am - 09:15 am	COMPLEX AND REDUNDANT MECHANISMS CONTROL HAIR FOLLICLE PATTERNING Sarah Millar
09:15 am - 10:00 am	SIGNALING NETWORKS OF HAIR FOLLICLES ACROSS SPATIAL SCALES Maksim Plikus
10:00 am - 10:05 am	INTERDISCIPLINARY OPPORTUNITY AWARD (IOA) ANNOUNCEMENT
10:05 am - 10:30 am	COFFEE BREAK Atrium
10:30 am - 11:15 am	MODELING INSIGHTS INTO SARS-COV-2 RESPIRATORY TRACT INFECTIONS Greg Forest
11:15 am - 12:00 pm	MOLECULAR ANALYSIS OF PROGENITOR AND STEM CELL STATES ACROSS HUMAN DEVELOPMENT AND SKELETAL MUSCLE April Pyle

12:00 pm - 01:30 pm	LUNCH & BREAK
	Outdoor Dining Terrace and Dining Room
01:30 pm - 02:15 pm	FROM GENOMICS TO THERAPEUTICS: SINGLE-CELL
	DISSECTION AND MANIPULATION OF DISEASE CIRCUITRY
	Manolis Kellis
02:15 pm - 03:00 pm	PREDICTING HETEROGENEITY, ADAPTATION AND INVASION
	IN THE TUMOR ECOSYSTEM
	Stacey Finley
03:00 pm - 03:20 pm	COFFEE BREAK
	Atrium
03:20 pm - 05:00 pm	CONTRIBUTED SHORT TALKS AND IOA TALKS
05:00 pm - 06:00 pm	POSTER SESSION AND RECEPTION
	Atrium and Lawn
06:00 pm - 08:00 pm	DINNER
	Outdoor Dining Terrace and Dining Room

EVENT PROGRAM

Friday, October 29

08:00 am - 08:30 am	BREAKFAST
08:30 am - 09:15 am	ELUCIDATING CANCER METABOLIC FLEXIBILITY: WHEN GENETIC AND METABOLIC STATES CONVERGE José Onuchic
09:15 am - 10:00 am	DYNAMICS OF A TRANSCRIPTIONAL BRAKE Stanislav Shvartsman
10:00 am - 10:30 am	COFFEE BREAK AND POSTER SESSION Atrium
10:30 am - 11:15 am	THE STRUCTURE OF PRE-BIFURCATION STATES IN CELL FATE DECISIONS DURING THE PROGRESSION OF THE NEURAL CREST LINEAGE Igor Adameyko
11:15 am - 12:00 pm	NEXT GENERATION TOOLS FOR TISSUE GENOMICS Fei Chen
12:00 pm - 01:30 pm	LUNCH & BREAK Outdoor Dining Terrace and Dining Room
01:30 pm - 02:15 pm	EXPLORING THE IMPACT OF GENOME REPLICATION ON REGULATORY VARIATION AND EPIGENETIC DRIFT THROUGHOUT THE LIFESPAN Tim Downing

02:15 pm - 04:00 pm

CONTRIBUTED SHORT TALKS AND IOA TALKS

04:00 pm

IOA ABSTRACT DUE, AND ADJOURN



ABSTRACTS

Thursday, October 28

COMPLEX AND REDUNDANT MECHANISMS CONTROL HAIR FOLLICLE PATTERNING Sarah Millar

TBD

SIGNALING NETWORKS OF HAIR FOLLICLES ACROSS SPATIAL SCALES Maksim Plikus

TBD

MODELING INSIGHTS INTO SARS-COV-2 RESPIRATORY TRACT INFECTIONS Greg Forest

Insights into the mechanisms and dynamics of human respiratory tract (HRT) infections from the SARS-CoV-2 virus can inform public awareness as well as guide medical prevention and treatment for COVID-19 disease. Yet, the complex anatomy and physiology of the HRT coupled with the

inability to sample diverse regions of the HRT pose fundamental roadblocks in understanding the connections between inhaled exposure to the SARS-CoV-2 virus, clearance versus onset of infection, and how infection can and cannot progress to alveolar pneumonia. It is a pure fluke of fate that my research group explored lung biology and disease for over 2 decades in an effort we call the UNC Virtual Lung Project, spanning many disciplines. For the past decade my group has explored how viruses "traffic" in mucosal barriers coating human organs, including the upper and lower respiratory tract, focusing on natural and synthetic antibody protection.

Then along came the novel coronavirus SARS-CoV-2, requiring a step back to build a pre-immune response baseline modeling platform, on top of which we have begun to superimpose interventions, from adaptive immune responses to vaccine-induced or engineered antibodies to antivirals, introduced either pre-exposure or at any stage of infection. The baseline platform incorporates: detailed anatomy and physiology of the HRT, and best evolving information about SARS-CoV-2 virions in airway surface liquids (ASL), including infectability of epithelial cells and kinetics of cell replication of infectious virions, throughout the HRT. Our platform is unique in that we explicitly account for the front line of respiratory defense: the mucus barrier coating all airways that traps inhaled insults to be propelled by waves of beating cilia toward the epiglottis to be swallowed. The baseline model simulates outcomes from inhaled deposition of SARS-CoV-2 in the HRT, and tracks the progression of infectious virions in the ASL and infected epithelial cells. We focus this lecture on insights gained to understand, mechanistically, two outcomes from exposure to SARS-CoV-2 and their respective likelihoods: a nasal / upper respiratory tract infection, and alveolar pneumonia.

This work is joint with Alex Chen, Cal State Dominguez Hills, Tim Wessler, U. Michigan and UNC, UNC colleagues Ronit Freeman, Sam Lai, Ric Boucher, and Ray Pickles, and UNC graduate students Kate Daftari, Kameryn Hinton, and Jason Pearson.

MOLECULAR ANALYSIS OF PROGENITOR AND STEM CELL STATES ACROSS HUMAN DEVELOPMENT AND SKELETAL MUSCLE April Pyle

Skeletal muscle is endowed with a remarkable ability to repair after injury due to the endogenous muscle stem cell called the satellite cell (SC), that expresses the key muscle stem cell transcription factor, Pax7. During development Pax7 is also critical for building muscle and eventually these

progenitor cells transition to quiescent SCs residing in the muscle stem cell niche. The molecular and functional differences between these two Pax7 cell states is not well understood in development or in adult muscle. We performed single cell, proteomic, metabolic mass spectrometry and correlated this quantitative view to in vivo functional analysis to determine how these cell states are controlled in both human development, in adult muscle and from Pax7 cells generated from human pluripotent stem cells. We identified that progenitor cells are very similar with regard to regulation by myogenic transcription factors but have very different cellular signaling, protein architecture and metabolic control. Functional analysis in mouse models revealed that progenitor cells have remarkable ability to generate new muscle but different abilities to repair muscle long term. Understanding molecular differences and functional outputs of progenitor and stem cell states will provide an improved understanding of how to modulate or transition between the two states in development and disease for use in regenerative medicine.

FROM GENOMICS TO THERAPEUTICS: SINGLE-CELL DISSECTION AND MANIPULATION OF DISEASE CIRCUITRY Manolis Kellis

Disease-associated variants lie primarily in non-coding regions, increasing the urgency of understanding how gene-regulatory circuitry impacts human disease. To address this challenge, we generate comparative genomics, epigenomic, and transcriptional maps, spanning 823 human tissues, 1500 individuals, and 20 mil-lion 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, some-times re-shaping our understanding. We find that Alzheimer's variants act primarily through immune pro-cesses, 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 var-iation, and genetic variation across healthy and diseased individuals to map genetic effects into epigenomic, transcriptional, and function changes at single-cell resolution, to recognize cell-type-specific diseaseassociated somatic mutations indicative of mosaicism, and to recognize multi-tissue single-cell effects of exercise and obesity. We expand these methods to electronic health records to recognize multiphenotype effects of genetics, environment, and disease, combining clinical notes, lab tests, and diverse data modali-ties despite missing data. We integrate large cohorts to factorize phenotypegenotype correlations to reveal distinct biological contributors of complex diseases and traits, to

partition disease complexity, and to stratify patients for pathway-matched treatments. Lastly, we develop massively-parallel, programmable and modu-lar technologies for manipulating these pathways by high-throughput reporter assays, genome editing, and gene targeting in human cells and mice, to propose new therapeutic hypotheses in Alzheimer's, obesity, and cancer. These results provide a roadmap for translating genetic findings into mechanistic insights and ulti-mately new therapeutic avenues for complex disease and cancer.

PREDICTING HETEROGENEITY, ADAPTATION AND INVASION IN THE TUMOR ECOSYSTEM Stacey Finley

TBD



ABSTRACTS

Friday, October 29

ELUCIDATING CANCER METABOLIC FLEXIBILITY: WHEN GENETIC AND METABOLIC STATES CONVERGE

José Onuchic

It has been becoming clear that both glycolysis and oxidative phosphorylation (OXPHOS) play critical roles in various types of cancer. This study aims to decipher the genetic and metabolic regulation of glycolysis and OXPHOS in cancer. In particular, through coupling a gene regulatory network model with the metabolic pathways it controls, we establish a theoretical framework to study the interplay between glycolysis and OXPHOS. Our model demonstrates a direct association between the activities of AMPK and HIF-1, master regulators of OXPHOS and glycolysis respectively, with the activities of three metabolic pathways: glucose oxidation, glycolysis and fatty acid oxidation (FAO). Moreover, cancer cells are able to acquire a hybrid metabolic state characterized by high AMPK/HIF-1/OXPHOS/glycolysis activities.

Guided by the model, we develop metabolic pathway signatures to quantify the activities of glycolysis, FAO and the citric acid cycle of tumor samples by evaluating the expression levels of enzymes involved in the corresponding processes. By applying the pathway signatures and our previously defined AMPK/HIF-1 signatures, we confirmed their association and the existence of a hybrid metabolic phenotype at both the tumor level and the single cell level. The association of AMPK/HIF-1 activity with metabolic pathway activity, predicted by the model and verified by analyzing the gene expression and metabolite abundance data of patient samples and single cells, was further validated by in vitro studies of aggressive triple negative breast cancer cell lines. In summary, we demonstrate a direct association of the AMPK/HIF-1 activity with metabolic pathway activity and investigate the existence of an aggressive hybrid metabolic phenotype.

DYNAMICS OF A TRANSCRIPTIONAL BRAKE

Stanislav Shvartsman

Even though transcriptional repressors are studied with ever-increasing molecular resolution, the temporal aspects of gene repression remain poorly understood. I will present our recent work on gene repression by Capicua (Cic), which is essential for development and is commonly mutated in human cancers. We determined the speed limit for Cic-dependent gene repression based on live imaging and optogenetic perturbations in the early Drosophila embryo, where Cic was originally discovered. Our measurements of Cic concentration and intranuclear mobility, along with real-time monitoring of the activity of Cic target genes, reveal that transcriptional repression sets in within minutes of removing an optogenetic de-repressive signal. In parallel, quantitative analyses of transcriptional bursting of Cic target genes support a repression mechanism providing a fast-acting brake on burst generation. This work sets quantitative constraints on potential mechanisms for gene regulation by Cic.

THE STRUCTURE OF PRE-BIFURCATION STATES IN CELL FATE DECISIONS DURING THE PROGRESSION OF THE NEURAL CREST LINEAGE

Most cell fate decisions are binary and are executed after a cryptic period of "decision-making". We investigated this period at the single cell level and found the co-presence of competing gene expression programs, which resolve the competition prior to the bifurcation point on a single cell trajectory. Thus, each branch of the decision tree goes through initial coactivation of bipotential properties and is followed by principal shifts toward commitment. Competing fate programs are coactivated before individual cells reveal fate-specific

phenotypic features. The final fate determination proceeds via increased synchronization of relevant programs and concurrent repression of competing fate programs."

NEXT GENERATION TOOLS FOR TISSUE GENOMICS Fei Chen

The precise spatial localization of molecular signals within tissues richly informs the mechanisms of tissue formation and function. Here, we'll introduce Slide-seq, a technology which enables transcriptome-wide measurements with near-single cell spatial resolution. We'll describe recent experimental and computational advances to enable Slide-seq in biological contexts in biological contexts where high detection sensitivity is important. More broadly, we'll discuss the promise and challenges of spatial transcriptomics for tissue genomics.

EXPLORING THE IMPACT OF GENOME REPLICATION ON REGULATORY VARIATION AND EPIGENETIC DRIFT THROUGHOUT THE LIFESPAN Tim Downing

Molecular heterogeneity is emerging as a critical feature of multicellular life. While singlecell analyses have revealed the existence of cell-to-cell variation in the levels and activities of the molecules responsible for gene regulation, the source of such variation is still poorly understood. The Downing Lab studies how genome replication contributes to epigenetic heterogeneity across stem cell populations. We recently developed new sequencing methods to measure epigenetic patterns in DNA methylation and chromatin accessibility within newly replicated strands of DNA over time. Using these methods, we find that genome replication introduces a window of epigenetic entropy that resolves over time within human embryonic stem cells (hESCs). We employ bioinformatic analyses to explore how properties of post-replication DNA methylation and accessibility dynamics relate to well-established features of the genome and the broader chromatin landscape as well as properties of gene expression and transcript composition. Our findings reveal that unique patterns of methylome replication associate with distal regulatory regions throughout the genome, enrich for cytosine residues dynamically methylated across cell types, and coincide with the location of stem cell-specific transcription factor binding and chromatin architectures. We also find correlations between sub-cell cycle kinetics in DNA methylation and the divergence of bulk methylation patterns observed during multiple cell generations and natural aging. Taken together, our studies suggest that (epi)genome replication may act as an important source of (temporal) regulatory variation in hESCs while, simultaneously, conferring susceptibility to epigenetic drift throughout the human lifespan.



CONTRIBUTED & IOA TALK SCHEDULE

Thursday, 10/28/2021

03:20 - 03:35	Long-Term Dna Recording with Ordered Insertion Mutations
	Theresa Loveless, University of California, Irvine
03:35 - 03:50	Inhibition of Phosphatidylinositol 3-Kinase During Spontaneous
	Differentiation of Human Induced Pluripotent Stem Cells Modulates Colony
	Self-Organization
	Arina Nikitina, Georgia Institute of Technology
03:50 - 04:05	Utilizing Stochasticity to Disambiguate Underlying Biological Mechanisms
	Linh Huynh, Case Western Reserve University
04:05 - 04:20	Identifying Gene Network Motifs Within Stochastically Transitioning
	Melanocyte Subclusters (IOA #1)
	Michael Caldwell, University of California, Irvine and Junhao Gu, University of
	California, Irvine
04:20 - 04:35	Region-Specific Amino Acid Metabolic Activities in Cutaneous Wounds
	(IOA #2)
	Johnny Le, University of Southern California and Remy Vu, University of
	Southern California
04:35 - 04:50	Learning the Interactions Driving Collective Motion in the Mitotic Spindle
	Christopher Miles, University of California, Irvine

Friday, 10/29/2021

02:15 – 02:30	Understanding How the Dynamic Mechanical Environment of The Heart
	Affects the Organization and Viability of Cardiac Cells (IOA #4)
	Ali Hetta, University of California, Irvine, Richard Tran, University of California,
	Irvine and Avraham Moriel, Weizmann Institute, Israel
02:30 – 02:45	Data Driven Mathematical Modeling of Single-Cell Gene Regulatory
	Dynamics in Alzheimer's Disease (IOA #3)
	Samuel Morabito, University of California, Irvine and Sohyeon Park, University of
	California, Irvine
02:45 - 03:00	Single-Cell Parameter Inference of Calcium Pathway Models
	Xiaojun Wu, University of Southern California
03:00 – 03:15	Dissecting Transition Cells from Single-Cell Transcriptome Data Through
	Multiscale Stochastic Dynamics
	Peijie Zhou, University of California, Irvine
03:15 – 03:30	Can Stochastic Fluctuations in Cell Cooperation Contribute to
	Carcinogenesis?
	Michael Caldwell, University of California, Irvine
03:30 – 03:45	Effects of Circuit-Host Interactions on Cell Fates and Control
	Xiaojun Tian, Arizona State University
03:45 – 04:00	Spectral and Lifetime Imaging for the Physiological Profiling of Living Cells
	Lorenzo Scipioni, University of California, Irvine



POSTERS PRESENTERS

Kwadwo Bonsu, University of California, Irvine Michael Caldwell, University of California, Irvine Yingxin Cao, University of California, Irvine Jinghao Chen, University of California, Irvine Emmanuel Dollinger, University of California, Irvine Joel Dorkmegang, Northwestern University Morgan Dragan, University of California, Irvine Junyan Duan, University of California, Irvine Alvaro Fletcher, University of California, Irvine Theresa Loveless, University of California, Irvine Michelle Ngo, University of California, Irvine Arina Nikitina, Georgia Institute of Technology Sohyeon Park, University of California, Irvine Moises Romero, University of California, Irvine Adam Stabell, University of California, Irvine Gessner Soto, University of Colorado - Denver Annie Trinh, University of California, Irvine Yifan Wang, University of California, Irvine Kirsten Wong, University of California, Irvine Xiaojun Wu, University of Southern California Lingyun Xiong, University of Southern California