HiTS

Harvard Program
in Therapeutic Science

HiTS Fall Symposium

Thursday, October 22, 2015

8:30 am - 6:00 pm

American Academy of Arts & Sciences, Cambridge, MA

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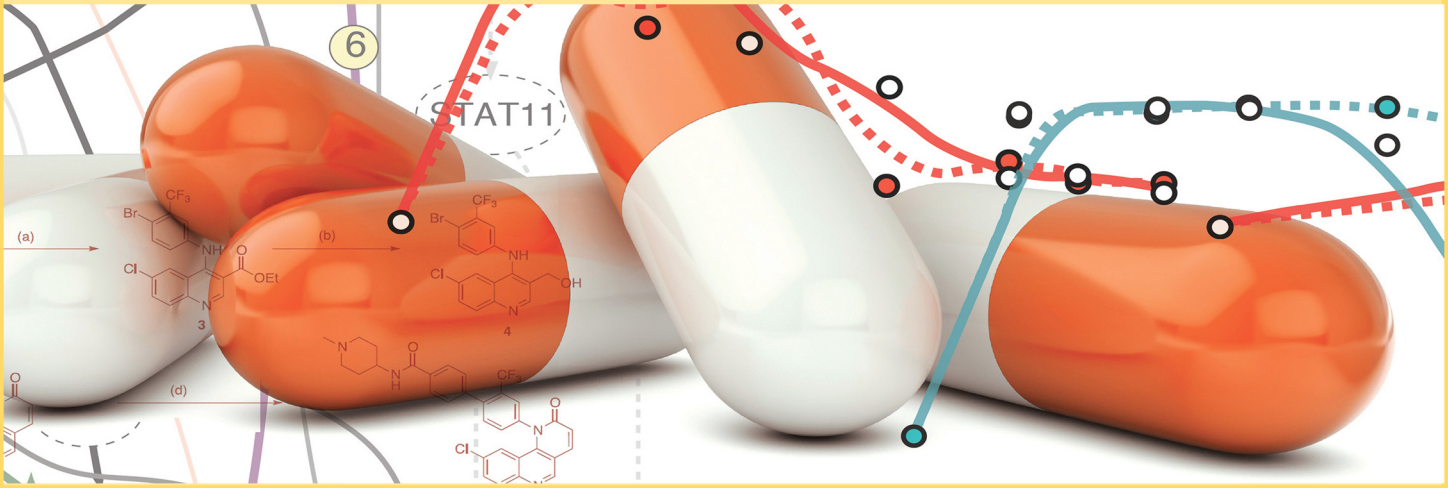

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Schedule

8:30 – 9:00am	Registration/Breakfast
9:00 – 9:15am	Preliminary Remarks – **Peter Sorger**, Head of HiTS, HMS
9:15 – 10:00am	Keynote Talk – **Eric Sobie**, Icahn School of Medicine at Mount Sinai *Exploiting mathematical models to understand differences between individuals in response to cardiac drugs*
10:00 – 11:30am	**Session 1: LSP Approach to Modeling and Informatics** **William Chen**, Chair **Ben Gyori**, LSP, Harvard Medical School **Mohammed AlQuraishi**, Systems Biology, Harvard Medical School **Murat Cokol**, Systems Biology, Harvard Medical School, Tufts University **Mike Springer**, Systems Biology, Harvard Medical School
11:30 – 11:45am	Coffee Break
11:45 – 12:45pm	**Session 2: Pharmacology of the CNS** **Tim Mitchison**, Chair **Bradley Hyman**, Massachusetts General Hospital **Stephen Haggarty**, Neurobiology, HMS, Massachusetts General Hospital **Randall Peterson**, Systems Biology, HMS, Massachusetts General Hospital
12:45 – 1:30pm	Lunch
1:30 – 2:45pm	**Session 3: Approaches to Clinical Translation** **Jagesh Shah**, Chair **Ralph Weissleder**, HMS, Massachusetts General Hospital **Doug Lauffenburger**, MIT **Dejan Juric**, Massachusetts General Hospital
2:45 – 3:00pm	Coffee Break
3:00 – 4:30pm	**Session 4: Measuring and Modeling Cellular Dynamics** **Galit Lahav**, Chair **Pamela Silver**, Harvard Medical School, Wyss Institute **Bree Aldridge**, Tufts University **Conor Evans**, Massachusetts General Hospital
4:30 – 6:00pm	**Poster Session with Refreshments**

LSP P50 Scientific Advisory Board Members

Jeremy Jenkins, Novartis

Jeremy L. Jenkins is global head of Developmental & Molecular Pathways Research Informatics (DRI) and Senior Investigator II at the Novartis Institutes for BioMedical Research in Cambridge, MA. He is responsible for the DRI teams comprised of Computational Biology, Computational Engineering, and Screening Informatics. He has worked at Novartis for more than 12 years in the fields of lead discovery, cheminformatics, chemogenomics and chemical biology, knowledge engineering, and network pharmacology. He was a Novartis postdoc from 2003-2005, following postdoctoral research at the Harvard Medical School in the Center for Biochemical & Biophysical Sciences and Medicine in the lab of Dr. Robert Shapiro, where he trained in HTS, virtual screening, and computer-aided drug design. He received his PhD in Molecular Genetics from The Ohio State University in 2000. Jeremy was the 2011 Corwin Hansch Award winner for contributions to the field of Quantitative Structure-Activity Relationships.

Bryan Roth, University of North Carolina School of Medicine

Bryan Roth MD, PhD is the Michael Hooker Distinguished Professor of Pharmacology at UNC Chapel Hill Medical School. He is a member of the National Academy of Medicine of the National Academy of Sciences.

Latest DREADD information: http://chemogenetic.blogspot.com/

Lab Home Page: http://pdspdb.unc.edu/rothlab/index.php

Eric Sobie, Icahn School of Medicine at Mount Sinai

Eric Sobie is Associate Professor in the Department of Pharmacology and Systems Therapeutics at Icahn School of Medicine at Mount Sinai. He received undergraduate and PhD degrees in Biomedical Engineering from Duke University and Johns Hopkins University, respectively, and he completed his postdoctoral training at the University of Maryland. In addition to running a research laboratory, he also directs a PhD program in Biophysics and Systems Pharmacology. His research focuses on uncovering mechanisms underlying cardiac dysfunction and arrhythmias by combining physiological experiments with mathematical modeling.

A.J. Marian Walhout, University of Massachusetts Medical School

Marian Walhout obtained her PhD in Biochemistry at Utrecht University in the Netherlands. She pursued post-doctoral research at Harvard Medical School and started her own lab at the University of Massachusetts Medical School in 2003

Her lab has pioneered gene-centered approaches for regulatory network studies, as well as interspecies systems biology studies to characterize the phenotypic and molecular responses to different nutrients, using the nematode C. elegans as a model. Marian co-authored a handbook on systems biology and is the co-director of the Program in Systems Biology at UMass Medical School.

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Keynote Talk Abstract

Exploiting mathematical models to understand differences between individuals in response to cardiac drugs

Eric Sobie

I will discuss recent efforts in my lab to gain insight into both therapeutic and detrimental effects of drugs in the heart. We obtain these new insights through Systems Pharmacology, combining experimental measurements with mechanistic simulations and statistical analyses of large data sets. I will discuss how we have used these approaches to understand differences between individuals in the response to drugs that cause arrhythmias, to identify targets that are anti-arrhythmic instead of pro-arrhythmic, and to develop novel methods to distinguish between safe drugs and harmful drugs.

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Poster Abstracts

#1 A multiscale statistical mechanical framework integrates biophysical and genomic data to assemble cancer networks

Mohammed AlQuraishi

Functional interpretation of genomic variation is critical to understanding human disease but it remains difficult to predict the effects of specific mutations on protein interaction networks and the phenotypes they regulate. We describe an analytical framework based on multiscale statistical mechanics that integrates genomic and biophysical data to model the human SH2-phosphoprotein network in normal and cancer cells. We apply our approach to data in The Cancer Genome Atlas (TCGA) and test model predictions experimentally. We find that mutations in phosphoproteins often create new interactions but that mutations in SH2 domains result almost exclusively in loss of interactions. Some of these mutations eliminate all interactions but many cause more selective loss, thereby rewiring specific edges in highly connected subnetworks. Moreover, idiosyncratic mutations appear to be as functionally consequential as recurrent mutations. By synthesizing genomic, structural, and biochemical data our framework represents a new approach to the interpretation of genetic variation.

#2 Multiplexed Exchange-PAINT imaging of RTKs reveals ligand-dependent EGFR and Met interactions in the plasma membrane

Verena Becker

Signal transduction by transmembrane receptors involves complex ligand- and time-dependent changes in conformation and modification state that lead to assembly of homo- and hetero-oligomers and larger aggregates (receptor clusters). In the case of receptor tyrosine kinases (RTKs) structural studies provide detailed data on individual receptor dimers but do not reveal how different RTKs are distributed or interact in the membrane. Studying such interactions is complicated by variable and often low receptor affinities and the inability of conventional microscopy to resolve nanoscale structures. We report the use of multiplexed super-resolution imaging (Exchange-PAINT) followed by mean-shift clustering and random forest analysis to measure the precise distribution of five receptor tyrosine kinases (RTKs) from the ErbB, IGF-1R and Met families that interact in breast cancer cells. Interestingly, these receptors are normally intermixed in a non-homogenous manner on the plasma membrane. Stimulation by EGF does not appear to induce a change in the density of EGFR in local clusters, implying that such clusters are largely preformed. Instead, ligand addition results in formation of non-canonical receptor pairs previously associated in drug resistance. These findings are supported by biochemical analysis, which demonstrates that our combined approach can find meaningful patterns in heterogeneous protein distributions on the nanoscale.

#3 High Throughput Identification of Apoptosis Sensitizing Chemicals on Freshly Isolated Tumor Cells

Patrick Bhola

Although dramatic improvements have been made in the treatment of breast cancer, there remains a need to identify new therapies to treat advanced tumors. While functional chemical screens for cell death using breast cancer cell lines has been an attractive approach for identifying novel therapeutics, it is increasingly clear that cell lines are not accurate representations of tumors. This fidelity gap between cell lines and the original tumor likely results in molecules that kills cancer cell lines though lack in vivo efficacy, or worse, may discard useful drugs that would indeed kill tumors, but not their derived cell lines. With the goal of closing this fidelity gap, we developed high throughput dynamic BH3 profiling (HT-DBP) – a functional and phenotypic method that determines whether short (< 20 hour) chemical library treatments on freshly isolated tumor cells increases the mitochondrial apoptotic sensitivity of those tumor cells. We performed HT-DBP on MMTV-PyMT mouse breast tumors using a panel of 2409 bioactive molecules. We found that 20 molecules in this library increased apoptotic sensitivity in freshly isolated tumor cells, but not in healthy human fibroblasts, thereby demonstrating a therapeutic window of these compounds. Importantly, 9 of these 20 compounds increased apoptotic sensitivity in freshly isolated tumor cells, but not in the derived cultured cell lines. The efficacy of these 9 compounds remains to be validated in mouse experiments. Nonetheless, our preliminary results indicate that HT-DBP may identify truly novel chemotherapies that have otherwise been excluded by conventional cell death screens on cancer cell lines.

#4 aRrayLasso: a network-based approach to microarray interconversion

Adam Brown

Summary: Robust conversion between microarray platforms is needed to leverage the wide variety of microarray expression studies that have been conducted to date. Currently available conversion methods rely on manufacturer annotations, which are often incomplete, or on direct alignment of probes from different platforms, which often fail to yield acceptable gene-wise correlation. Here, we describe aRrayLasso, which uses the Lasso-penalized generalized linear model to model the relationships between individual probes in different probe sets. We have implemented aRrayLasso in a set of five open-source R functions that allow the user to acquire data from public sources such as GEO, train a set of Lasso models on that data, and directly map one microarray platform to another. aRrayLasso significantly predicts expression levels with similar fidelity to technical replicates of the same RNA pool, demonstrating its utility in the integration of data sets from different platforms.

Availability and Implementation: All functions are available, along with descriptions, at https://github.com/adam-sam-brown/aRrayLasso.

#5 The systems toxicology efforts in kidney damage

Mariana Cardenas, Mira Pavkovic, Susanne Ramm

Drugs and environmental chemicals are a common cause of kidney injury in humans, posing a significant health burden for patients and a financial risk for pharmaceutical companies. In addition, acute injury often results in chronic kidney disease, which has a prevalence of 8-16% worldwide.

However, a regulatory accepted or validated in vitro model to screen for kidney toxicants is still missing and there are no sensitive and specific biomarkers available for the early detection of kidney disease in patients.

To overcome these limitations, we are pursuing two main aims: 1. A quantitative systems pharmacology approach to develop predictive models that identify and classify toxic compounds and their mechanisms; 2. The discovery and evaluation of new microRNA biomarkers using urine samples from large clinical studies (cross-sectional and longitudinal), enrolling up to 500 patients with various etiologies of kidney disease.

The successful completion of these projects has the potential to result in a paradigm shift in the prediction and management of kidney toxicity and to improve public health.

#6 Ethambutol: one drug too many in tuberculosis combination therapy?

Murat Cokol

M. tuberculosis infections claim more than one million lives a year. Treatment for tuberculosis requires at least six months of antibiotic treatment with a drug cocktail that includes rifampicin, isoniazid and ethambutol. Drugs in combination can have surprisingly high or low efficacy given the effect of constituent drugs, in phenomena known as drug interactions. In this study, we measured the pairwise interactions of standard tuberculosis antibiotics in the model organism M. smegmatis. We found that while rifampicin and isoniazid have increased efficacy when combined (drug synergy), combinations involving ethambutol were antagonistic. In addition, we observed that the inclusion of ethambutol leads to antagonism in the three-drug combination. Next, we conducted a sensitive screen to discover antibiotics that have increased efficacy when combined with rifampicin or isoniazid. We found that ethionamide, a second-line antibiotic used against M. tuberculosis infections unresponsive to the standard regimen, was synergistic with isoniazid and additive with rifampicin. We experimentally confirmed the synergistic interaction of the three-drug combination rifampicin+isoniazid+ethionamide. We are currently in the process of testing this combination therapy in M. tuberculosis.

#7 Systematic Analysis of RAF/MEK-Targeted Therapy-Induced Adaptive Resistance in Melanoma

Mohammad Fallahi-Sichani

#8 Systems Biology of Polycystic Kidney Disease

Kelly George

Polycystic kidney disease (PKD) is a group of hereditary disease states characterized by cystic kidneys and often accompanied by other manifestations such as cystic liver and hypertension. PKD occurs in 1 in 500 people, usually resulting from a dominant mutation in one of two genes, PKD1 or PKD2. There are currently no treatments for PKD and it is the leading genetic cause of renal failure. Numerous studies have identified many pathways that are misregulated in PKD but targeting these individual pathways has not led to a successful therapeutic intervention or molecular biomarker. The only biomarkers for PKD are total kidney volume and the functional glomerular filtration rate, which are lagging indicators of disease status.

To identify potential biomarkers and develop a systems-level understanding of PKD, we are using transcriptomics, and quantitative proteomics and phospho-proteomics to evaluate the state of cystic and normal kidneys in a mouse model of PKD throughout cystogenesis. Kidney cysts also induce injury to the surrounding tissues, confounding any analysis of the "cystic state". In an effort to separate the injury signature from the cystic signature, we are also evaluating the state of the injured kidney using a folate model of acute kidney injury. From the transcriptomic experiments, we have generated a list of potential biomarkers in addition to a set of genes that correlate with the cystic state of the kidney. The multi-kinase inhibitor Roscovitine has been shown to prevent cystogenesis in multiple mouse models of PKD but the mechanism of action remains unknown. To gain insight into the mechanism(s) of Roscovitine and to identify biomarkers that change with treatment, we are also using the above –omic strategies using kidneys from mice following treatment. Phosphorylation at motifs for CDKs, CK1, CaMK, and others are reduced in kidneys treated with Roscovitine. The primary transcription factor family found to be suppressed with Roscovitine treatment is the E2Fs, likely a result in the loss of CDK signaling.

#9 Application of Small RNA Sequencing to Identify MicroRNAs in Acute Kidney Injury and Fibrosis

Cory Gerlach

Establishing a microRNA (miRNA) expression profile in affected tissues provides an important foundation for the discovery of miRNAs involved in the development or progression of pathologic conditions. We conducted small RNA sequencing to generate a temporal profile of miRNA expression in the kidneys using a mouse model of folic acid-induced (250 mg/kg i.p.) kidney injury and fibrosis. From the 103 miRNAs that were differentially expressed over the time course (>2-fold, $p<0.05$), we chose to further investigate miR-18a-5p, which is expressed during the acute stage of the injury; miR-132-3p, which is upregulated during transition between acute and fibrotic injury; and miR-146b-5p, which is highly expressed at the peak of fibrosis. Using qRT-PCR, we confirmed the increased expression of these candidate miRNAs in the folic acid model as well as in other established mouse models of acute injury (ischemia/reperfusion injury) and fibrosis (unilateral ureteral obstruction). In situ hybridization confirmed high expression of miR-18a-5p, miR-132-3p and miR-146b-5p throughout the kidney cortex in mice and humans with severe kidney injury or fibrosis. When primary human proximal tubular epithelial cells were treated with model nephrotoxicants such as cadmium chloride ($CdCl_2$), arsenic trioxide, aristolochic acid (AA), potassium dichromate and cisplatin, miRNA-132-3p was upregulated 3.5-fold after AA treatment and 1.5-fold after $CdCl_2$ and cisplatin treatment. These results demonstrate the application of temporal small RNA sequencing to identify miR-18a, miR-132 and miR-146b as differentially expressed miRNAs during distinct phases of kidney injury and fibrosis progression.

#10 Automated assembly of pathway models from natural language and databases with INDRA

Benjamin M. Gyori

INDRA is a software tool that takes natural language descriptions of molecular mechanisms from a user and automatically generates a quantitative simulation model from it.

INDRA also provides access to published literature and pathway databases to add additional mechanisms to the model.

This allows rapid model building with minimal expertise in modeling formalisms and mathematics. As an example, we show a computational model automatically generated from a natural language description of EGFR signaling.

#11 Drug response metrics based on growth rate inhibition correct for the confounding effects of division rate

Marc Hafner

The drug response metrics IC50 and Emax are widely used in cancer biology but suffer from a fundamental flaw when applied to growing cells: they are highly sensitive to the number of divisions that take place over the course of a response assay. Division rate varies with cell line and experimental conditions; seeding density is a particularly strong and unpredictable confounder. The dependency of IC50 and Emax on division rate creates artefactual correlations between properties of cell lines (e.g. genotype) and drug sensitivity while obscuring important biological insights. In this paper we derive alternative drug response metrics that are insensitive to division number. These are based on estimating growth rate inhibition (GR) in the presence of drug using endpoint or time-course assays, the latter of which provide a direct measure of phenomena such as adaptive drug resistance. Theory and experiments show that GR50 and GRmax should replace IC50 and Emax when assessing drugs that affect cell division; making this change requires only modest modifications to experimental protocols. We expect GR metrics to improve pre-clinical pharmacology and precision therapeutic assays employing patient-derived tumor cells.

#12 Highly multiplexed single-cell imaging of growth factor signalling reveals shared drug response axes and signalling adaptations

Saman Honarnejad

In drug discovery, utilization of high-throughput screening (HTS) of chemicals has drastically increased the number of agents entering early clinical trials. However, most lead compounds that pass medicinal chemistry studies fail to pass clinical phases, typically due to lack of potency or safety. Here, we propose an automated high-content immunofluorescence (IF) imaging combined with a highly multiplexed cyclic immunofluorescence (CycIF) single-cell imaging method instead of conventional HTS techniques that only use bulk measurements of population average to address issues of potency and efficacy of chemical agents early in preclinical studies. In this study, we show the power of image-based high-dimensional single-cell profiling in investigating heterogeneity of phenotypic states across drugs with similar and different targets. Specifically, we show that drugs with similar targets have common response profile and provide evidence towards fractional response to mTOR targeting drugs by induction of S/G2 cell cycle phase transition through upregulation of ERK/RB signalling and downregulation of p21/Cip1 levels. In addition to the innovative pipeline for data generation, we provide examples for analysis and visualization of such highly multiplexed high-dimensional single-cell drug screen data that could benefit the preclinical drug discovery community to use as a framework to select for lead compounds with less risk of failure in late developmental phase.

#13 Single cell imaging of kinase inhibitor-induced effects in breast cancer cell lines

Caitlin Mills

Six breast cancer cell lines representing triple negative, hormone receptor positive, and Her2 amplified disease were treated with a panel of 108 kinase inhibitors. Cells were stained with DRAQ5 (DNA) and TMRE (mitochondrial membrane potential), and images were acquired using a high throughput, confocal Opera microscope 24 hours after treatment. Cell segmentation and feature extraction (intensity, morphology, and texture) were performed with Acapella software. Over 300 features were extracted for ~1.5 million cells. Analytical methods have been applied to identify those treatments that induced significant changes to the cells with the goal of identifying cell line and pathway specific effects.

#14 Antiapoptotic defense evolution in cancer: novel therapeutic strategies to restore cell death using Dynamic BH3 profiling.

Joan Montero, Dorota E. Sadowicz, Rizwan Haq*, Anthony Letai*

* authors contributed equally

Background: There is a lack of effective predictive biomarkers to efficiently assess the optimal treatment for each patient and overcome resistance. When effective death signaling is initiated by a targeted therapy, an increase in mitochondrial apoptotic sensitivity (or 'priming for death') can be observed within hours with Dynamic BH3 Profiling (DBP). Most chemotherapeutic agents kill via the mitochondrial pathway of apoptosis, but unfortunately tumors frequently are able to survive adapting their antiapoptotic strategy. By using different BH3 peptides we can determine the tumor's defense adaptation over time and find novel ways to overcome resistance using BH3 mimetics restoring cell death.

Hypothesis: Analyzing the tumor's antipoptotic defense over time with DBP we can predict how the tumor will adapt to the first-line therapy and restore cell death using BH3 mimetics.

Results: Our first set of experiments consisted in characterizing the tumor's adaptation to therapy over time. We performed DBP over time using different BH3 peptides: BIM, BAD, MS1, PUMA and NOXA. In GIST and melanoma cell lines, we observed that when they were effectively treated with imatinib (BCR-ABL inhibitor) and dabrafenib (BRAFV600E inhibitor) respectively, or to selumetinib (MEK inhibitor) in both cases, there was an increased dependence in MCL-1 between 24 and 48 hours. This observation explains a possible mechanism by which tumors become resistant to first-line treatment, adapting their antiapoptotic strategy to overcome chemotherapy. Based on these observations, we tested novel ways to overcome this resistance by pretreating the cancer cells with the above mentioned targeted therapies and then add a specific MCL-1 inhibitor to restore cell death. Other cell lines, including breast cancer and melanoma, were subsequently studied, and the combination of specific targeted therapies with BH3 mimetics (ABT-199, ABT-263 and MCL-1 inhibitors) was also assessed.

Exploiting DBP's capacity to measure changes in priming without the requirement for prolonged ex vivo culture, we assessed if this antipoptotic evolution was also present in primary melanoma samples. We tested combinations of targeted therapies with BH3 mimetics to identify novel therapeutic strategies to overcome resistance to treatment in this type of solid tumors.

Conclusions: Our cell line and clinical experiments demonstrate the potential for Dynamic BH3 profiling to be used as a powerful real-time tool to predict chemotherapy response and overcome resistance in relapsed patients, by studying combinations of targeted agents with BH3 mimetics.

#15 Controlling Regulatory Tcell heterogeneity by chemical modification of signaling pathways

Nienke Moret

Regulatory Tcells (Tregs), a subtype of the CD4 Tcell pool, provide negative feedback to the immune system and are critical for homeostasis of the immune response. To perform their function, Tregs communicate with various cell types through different molecular interactions. Upon activation of a seemingly homogenous naïve splenic Treg pool, a heterogeneous ensemble of specialized activated cells arises, each specialization expressing a different set of functional cell-surface proteins.

We use chemical genetics to systematically modify signaling pathways in splenic Tregs to determine how different signaling cascades contribute to the heterogeneity in activated Tregs. Specifically, we use a library of well-characterized kinase inhibitors, allowing us to tightly regulate pathway activity. We completed a pilot screen of 40 compounds, measuring the changes in expression of five cell surface proteins (CD69, CD25, ICOS, GARP and TIGIT) following treatment. Here, we see that different inhibitors not only influence the level of expression, but also change the relationships between proteins. We developed a computational tool that quantifies the changes in expression of the measured proteins and the correlations between them, resulting in a similarity score of the treated cell populations versus the DMSO control population.

By combining this similarity score with the absolute intensities of the markers, we will determine how the specialized activated Treg phenotypes cluster in multidimensional space and how cluster occupancy changes upon treatment. Subsequently, we will map the kinase inhibitors to their targets, taking polypharmacology into account. We will use various cheminformatics tools to classify the compounds by pathway, considering that specific conformations induced by the chemical probes can lead to significant crosstalk between pathways. The ultimate goal of this work is to develop a probability model to elucidate which signaling cascades are involved in creating the heterogeneous Treg pool.

#16 Quantifying Drug Dose Response and Resistance from Cell Cycle Deformations

Satabhisa Mukhopadhyay

A quantitative framework for drug dose response/drug resistance, that works with sufficient degree of reproducibility across cell-types, drug types, doses, treatment time and combinations there of, should be able to quantitatively predict branching of cell cycle fluxes among various weird pockets and nested sub-cycles of deformed cell cycle that those treatment conditions give rise to. We present a differential mutual information flow based framework that can quantitatively predict such bifurcated paths in deformed cell cycles across spectra of drug dose response landscapes which is further studied mechanistically to tease out quantitative variabilities among those paths. The power of this method is that it retrieves inherent cell cycle time from data and hence is capable of quantitatively reading out the hierarchy of mechanistic effects in terms of branching times. This method is also capable of giving rise to a differential mutual information flow based quantitative score for drug dose response/drug resistance 'effectiveness'.

#17 The roles of synergy and cross-resistance in combination chemotherapy

Adam Palmer

Monotherapies are often effective for only a short duration because of the evolution of drug resistance, while more durable, sometimes even curative outcomes can be obtained with combination themotherapies. Which interaction properties amongst the therapies in a combination are most conducive to clinical efficacy? A common goal of pre-clinical combination studies is 'synergy', indicating a combination whose potency is greater than the sum of its parts. Here we study an examplar of effective combination therapy, R-CHOP, which achieves curative outcomes for many patients with Non-Hodgkin Lymphoma. We quantified the interactions between all pairings of these different therapies and found that none showed synergy, and indeed many demonstrated antagonism, the opposite effect. However, simple theoretical considerations indicate that synergy is likely to be less important in the design of combinations than is finding combinations with non-overlapping mechanisms of drug resistance, such that mutants with resistance to one component in a combination remain sensitive to at least one other component. Previously measurements of such 'cross-resistance' interactions have been extremely low throughput, but here we describe a DNA-barcoding based approach to systematically measure cross-resistance interactions amongst therapies by tracing the survival of many drug resistant lineages in parallel when treated with a variety of single therapies. High-throughput measurement of cross-resistance interactions between anti-cancer therapies should provide critical data in the assessment of potential combinations and facilitates a novel perspective on the rational design of combination therapies.

#18 Discovery of Small Molecules to Treat Sarcopenia

Feodor Price

The functional and structural decline of skeletal muscle is one of the first hallmarks of aging in many organisms. The growth, maintenance, and regeneration of skeletal muscle is attributed to the satellite cell: a mitotically quiescent stem cell that resides between the basal lamina and sarcolemma of the muscle fiber. Intriguingly, as an organism ages, a decrease in satellite cell numbers accompanies and partially accounts for deteriorating skeletal muscle function. To explore a potentially new method for slowing the decline in skeletal muscle function, we established a screen capable of identifying small molecules or biologicals that promote the proliferation of satellite cells. We discovered multiple compounds that display a cell autonomous effect in increasing satellite cell numbers and do so in the nM concentration range. Following subcutaneous injection of some of these compounds, mice following cardiotoxin-induced muscle injury displayed an increase in the number of total satellite cells, an increase in expression of the satellite cell marker Pax7 and the cross sectional area of regenerating fibers. Furthermore, we confirmed the ability of our compounds to promote proliferation of satellite cells from aged mouse muscle and from human skeletal muscle, while having no effect on fibroblast proliferation. Taken together, our results provide compelling evidence that small molecule screens provide a viable method to identify biologically relevant compounds with the potential to treat a variety of skeletal muscle disorders.

#19 Mathematical model of DISC assembly in TRAIL-mediated apoptosis

Kartik Subramanian

#20 Mechanistic hypothesis for the anti-inflammatory drug colchicine

Jui-Hsia Weng

Microtubule (MT) is one of the crucial features in cells and related to many cellular events. While roles of MT during cell division are well defined, it is not known how MT functions in non-dividing cells. Colchicine, a MT-targeting drug, rescues patients with inflammatory disorders via unclear mechanisms outside mitosis. Based on colchicine kinetic distribution, I propose that the non-proliferating liver hepatocyte is the main target of colchicine. To address if and how colchicine-blocked MT dynamics in liver cause whole-body anti-inflammatory effects, I will initially use primary cultured hepatocytes as a model to dissect signaling pathways, gene expression, and secreted proteins upon colchicine treatment. I will then study how perturbing MTs lead to these changes. I will then investigate how the communication between liver and white blood cells happens and identify the future implication for therapy improvement.