



Network Biology 2.0

Connecting Genomes to Disease Progression and Drug Response

THE BROAD INSTITUTE, 7 CAMBRIDGE CENTER, CAMBRIDGE, MA, 02142

APRIL 14-15, 2010

SCHEDULE OF EVENTS: APRIL 14, 2010

8:00 AM	<i>Continental Breakfast</i>
9:00	Welcome, Opening Remarks and Overview of the Day Iya Khalil, PhD <i>Conference Chair, Executive Vice President and Co-Founder of Gene Network Sciences</i>
9:10	Technologies for Collecting and Integrating Genome, Environment and Trait Data George Church, PhD <i>Professor of Genetics, Director of the Center for Computational Genetics, Harvard Medical School</i>
9:45	Real Time DNA Sequencing From Single Polymerase Molecules Stephen Turner, PhD <i>Founder and Chief Technology Officer, Pacific Biosciences</i>
10:20	Interactome Networks and Human Disease Marc Vidal, PhD <i>Professor of Genetics, Harvard Medical; Director, Center for Cancer Systems Biology</i>
10:55	<i>Coffee Break & Espresso Bar</i>
11:15	Conference Keynote: Malignant Progression and the Stem Cell State Robert A. Weinberg, PhD <i>Member, Whitehead Institute; Professor of Biology, MIT</i>
12:00 PM	<i>Lunch - Assorted Gourmet Sandwiches</i>

1:00	<p>Network Biology and Drug Discovery</p> <p>James J. Collins, PhD <i>Howard Hughes Medical Institute, Boston University and Harvard University</i></p>
1:35	<p>Using Network Models to Integrate Clinical and Molecular Data in Drug Development</p> <p>John Carulli, PhD <i>Director, Genetics and Genomics, Biogen Idec</i></p>
2:10	<p>Phosphodynamics of Receptor Tyrosine Kinase Signaling</p> <p>Peter Sorger, PhD <i>Professor of Systems Biology, Harvard Medical School ; Professor of Biological Engineering, MIT</i></p>
2:45	<p><i>Coffee Break & Espresso Bar</i></p>
3:05	<p>Systems-Based Approaches to Developing Rational Combination Therapies for Cancer</p> <p>W. Michael Korn, MD <i>Associate Professor of Medicine and Co-Director, Center of Molecular Oncology, Helen Dill Family Comprehensive Cancer Center at UCSF</i></p>
3:40	<p>Signatures for Small Molecule Discovery</p> <p>Todd Golub, MD <i>Founding Member, Director of Cancer Program, Broad Institute; Professor, Dana-Farber Cancer Institute</i></p>
4:15	<p>Molecular Characterization of Circulating Tumor Cells</p> <p>Daniel A. Haber, MD, PhD <i>Director, Massachusetts General Hospital Cancer Center; Harvard Medical School; Howard Hughes Medical Institute</i></p>
4:50	<p>Oncology Panel: New Approaches to Tackling Cancer</p> <p>Moderator: Alexis Borisy, <i>Entrepreneur in Residence, Third Rock Ventures</i> Panel: Todd Golub, MD, Michael Korn, MD, Daniel A. Haber, MD, PhD</p>
5:50	<p><i>Reception - Selection of Gourmet Appetizers and Beverages</i></p>
7:00	<p>Genomic Approaches to Cancer Patient Stratification</p> <p>William R. Sellers, MD <i>Vice President and Global Head of Oncology, Novartis Institutes for BioMedical Research</i></p>
7:35	<p><i>Day 1 Concludes</i></p>



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APRIL 14-15, 2010

SCHEDULE OF EVENTS: APRIL 15, 2010

7:30 AM	<i>Continental Breakfast</i>
8:30	Welcome and Overview of the Day Iya Khalil, PhD <i>Conference Chair, Executive Vice President and Co-Founder of Gene Network Sciences</i>
8:35	Interrogating Cancer Interactomes to Optimize Therapy on an Individual Basis Andrea Califano, PhD <i>Professor of Biomedical Informatics, Columbia University</i>
9:10	From Mitochondrial Parts and Pathways to Pathogenesis Vamsi Mootha, MD <i>Associate Professor, Harvard Medical School, Department of Systems Biology; Mass General Hospital Center for Human Genetic Research; Broad Institute</i>
9:45	Comparative Epigenomic Analysis of Cellular Differentiation Tarjei S. Mikkelsen, PhD <i>Post Doctoral Associate, Broad Institute</i>
10:20	<i>Coffee Break & Espresso Bar</i>
10:50	Spontaneous Cancer Cell Quiescence: A New Paradigm Sridhar Ramaswamy, MD <i>Assistant Professor of Medicine, Massachusetts General Hospital Cancer Center; Harvard Medical School; Broad Institute, Harvard Stem Cell Institute</i>
11:25	Unbiased Reconstruction of Mammalian Regulatory Networks Aviv Regev, PhD <i>Early Career Scientist, Howard Hughes Medical Institute; Core Member, Broad Institute; Assistant Professor of Biology, MIT</i>

12:00 PM	<i>Lunch - Assorted Gourmet Sandwiches</i>
1:00	<p>BRAF Expands the Frontier of Oncogene Targeted Therapy</p> <p>Keith Flaherty, MD <i>Director of Developmental Therapeutics, Cancer Center, Massachusetts General Hospital</i></p>
1:35	<p>Moving Towards an Understanding of the Molecular Networks Underlying Biological Hydrogen Production by Bacteria</p> <p>Eric E. Schadt, PhD <i>Chief Scientific Officer, Pacific Biosciences</i></p>
2:10	<p>Web-Based, Parallel Genome-Wide Association Studies: From Social Networks to Gene Networks</p> <p>Nicholas Eriksson, PhD <i>Principle Scientist: Statistical Genetics, 23andMe</i></p>
2:45	<i>Coffee Break & Espresso Bar</i>
3:20	<p>e-Health from the Ground Up: The Building of the King Hussein Institute for Biotechnology and Cancer in Amman, Jordan</p> <p>Eric Perakslis, PhD <i>Vice President, R&D Informatics Center of Excellence, COSAT, Johnson & Johnson Pharmaceuticals Research and Development</i></p>
3:55	<p>Research 2.0: How Social Networks, Clouds and Consumers Will Reshape Research</p> <p>Linda Avey <i>Founder, Brainstorm Research Foundation</i></p>
4:30	<p>Applied Phenomics: Insights from the PatientsLikeMe System</p> <p>James Heywood <i>Co-Founder and Chairman, PatientsLikeMe</i></p>
5:05	<p>Health 2.0 Panel: How will eHealth and Consumer Genetics Transform Translational Research and Medicine?</p> <p>Moderator: Kevin Davies, <i>Editor-In-Chief, Bio-IT World</i> Panelists: Linda Avey, Mark Boguski, MD, PhD, Nicholas Eriksson, PhD, James Heywood, and Eric Perakslis, PhD</p>
6:05	<i>Conference Concludes</i>

Linda Avey

Founder, Brainstorm Research Foundation

RESEARCH 2.0: HOW SOCIAL NETWORKS, CLOUDS AND CONSUMERS WILL RESHAPE RESEARCH

The advent of wildly popular social networks, and the apparent willingness of consumers to share information via these platforms, suggests a new model for conducting research that shifts the focus to the individuals- aka research subjects- from whom vitally important phenotypic information can be gained. Brainstorm Research Foundation is testing this new 'Research 2.0' model, with a focus on brain health.

Andrea Califano, PhD

Professor of Biomedical Informatics, Columbia University

INTERROGATING CANCER INTERACTOMES TO OPTIMIZE THERAPY ON AN INDIVIDUAL BASIS

The identification of genes acting synergistically as master regulators of physiologic and pathologic cellular phenotypes is a key open problem in systems biology, Here we use a molecular interaction based approach to identify the repertoire of transcription factors (TFs) of a master regulatory module responsible for synergistic activation of a tumor-specific signature. Specifically, we used the ARACNe algorithm and other computational tools to infer regulatory interactions responsible for initiating and maintaining the mesenchymal phenotype of Glioblastoma Multiforme (GBM), previously associated with the poorest disease prognosis. Expression of mesenchymal genes is a hallmark of aggressiveness but the upstream regulators of the signature are unknown. Starting from the unbiased analysis of all TFs, we identify a highly interconnected module of six TFs jointly regulating >75% of the genes in the signature. Two TFs (Stat3 and C/EBPb), in particular, display features of initiators and master regulators of module activity. Biochemical validation confirms that the TFs in the module bind to the inferred promoters in vivo and ectopic expression of the master TFs activates expression of the mesenchymal signature. These effects are sufficient to trigger mesenchymal transformation of neural stem cells, which become highly tumorigenic in vivo, and promote migration and invasion. Conversely, silencing of Stat3 and C/EBPb in human glioma cells leads to collapse of the mesenchymal signature and reduction of tumor aggressiveness. Our results reveal that activation of a small transcriptional module is necessary and sufficient to induce a mesenchymal phenotype in malignant brain tumors.

John Carulli, PhD

Director of Genetics and Genomics, Biogen Idec

USING NETWORK MODELS TO INTEGRATE CLINICAL AND MOLECULAR DATA IN DRUG DEVELOPMENT

Clinical trials offer unique opportunities to study human biology in a reasonably controlled setting. Integration of clinical and molecular data from human trials is increasingly used for biomarker and drug target discovery. To identify potential target pathways and biomarkers for Rheumatoid Arthritis (RA), we collected genetic, molecular and clinical data for a small trial of TNF inhibitors. Tumor necrosis factor-alpha is a key regulator of inflammation and rheumatoid arthritis (RA). TNF inhibitors are highly effective treatments for many RA patients, but are not effective in approximately one-third of patients. To identify biological pathways active in non-responders to TNF blockade, we used an approach that incorporates reverse-engineering and simulating in silico network disease models for rheumatoid arthritis. We collected genome-wide SNP and gene expression data, together with clinical measurements of disease activity, and used the data to build and simulate unbiased computer models of RA that were learned from variation in the genetic and genomic data. The models were built utilizing inference algorithms rather than correlative relationships extracted by traditional statistical methods. Two models were created, representing both TNF-alpha-dependent (before TNF α blockade) and TNF-alpha-independent (after TNF α blockade) molecular networks for rheumatoid arthritis. By simulating outcomes on a patient-specific basis, a virtual clinical trial was effected to systematically identify genes that are causal drivers of RA clinical measurements across patients. From these data-driven models that required no assumptions about the network biology, we identified several pathways as potential targets for patients unresponsive to TNF inhibition, including the clinically validated T cell co-stimulation pathway that is the target of the FDA approved drug abatacept. This discovery validates the network biology approach to clinical trials, and identifies additional biological pathways for drug discovery and development.

George Church, PhD

Director of the Center for Computational Genetics, Harvard Medical School

TECHNOLOGIES FOR COLLECTING AND INTEGRATING GENOME, ENVIRONMENT AND TRAIT DATA

The human genome draft completed in 2004 (at 8-fold coverage) was a milestone, but at \$3 billion it was not applicable to routine research or diagnostics. Expensive "common variant" association studies also generally failed to produce highly predictive and actionable diagnostics. Since 2004, we have pushed the cost of sequencing down by over a million-fold to about \$2000 per 40-fold genome today¹. This also enables time-series studies of epigenomic and immunogenomic responses to cancers, microbes, allergens, vaccines, etc. Sharing personal fibroblasts and stem cell lines and associated genome, environment and trait (GET) data greatly enables commercial and academic research, open-source software and data for interpreting whole and partial genome sequences² as well as community tools for diverse phenomics. As the utility of cells, genes, and traits increases, insights come from highly integrative approaches - evaluating individuals in cohorts holistically and computationally- often from outside the clinical specialty of the study, e.g. computer scientists, systems biologists, or educational communities. Progress has been made by consenting volunteers with the understanding of full disclosure³ (including tests of comprehension of the consenting materials). Technologies for analysis of single-chromosome haplotypes and single-cell epigenomics include dilution libraries and in situ sequencing.

1. Drmanac, R, et al. 2010 <http://www.sciencemag.org/cgi/data/1181498/DC1/1>, table S5
2. <http://snp.med.harvard.edu>, <http://evidence.personalgenomes.org/about>
3. Lunshof JE, Chadwick R, Vorhaus DB, Church GM. From genetic privacy to open consent. Nat Rev Genet. 2008 9:406-11. <http://personalgenomes.org>

Nicholas Eriksson, PhD

Principle Scientist: Statistical Genetics, 23andMe

TECHNOLOGIES FOR COLLECTING AND INTEGRATING GENOME, ENVIRONMENT AND TRAIT DATA

A significant challenge in the pursuit of the genetic basis of human traits and diseases has been the coordinated collection of genetic and non-genetic data. At 23andMe, we are connecting people with each other and with interpretations of their genetic data. We harness the resulting excitement to perform research on the genetic basis of hundreds of conditions ranging from Parkinson's disease to extroversion to how much mosquitoes bother you.

I'll present new genetic associations for a number of traits including some well-studied and some never before explored with genome-wide data. I'll talk about how this model of research can be useful for recruitment of cohorts and how the collection of multiple phenotypes for a large cohort raises exciting possibilities for systems biology.

Keith Flaherty, MD

Director of Developmental Therapeutics, Massachusetts General Hospital Cancer Center

BRAF, THE MOST PREVALENT ONCOGENE TO BE SUCCESSFULLY TARGETED

Therapy for advanced melanoma has progressed slowly over the past three decades. The successful translation of therapies targeting signal transduction pathways that are activated by oncogenes in other cancers has provided a model for molecularly targeted therapy.

The identification of *BRAF* mutations in 2002 was the watershed event that turned the attention of the melanoma field to this concept. Seven years passed between the identification of *BRAF* mutations and the validation of this target in melanoma patients with a potent and specific *BRAF* inhibitor, PLX4032. In the first-in-human trial, 49 of 55 patients enrolled in the dose escalation portion of the study had metastatic melanoma. There was enrichment for patients with ^{V600E}*BRAF* mutations as many patients' tumors were prospectively evaluated prior to study entry, particularly at the higher dose levels. An additional 32 patients with metastatic melanoma harboring *BRAF* mutations were enrolled at the maximum tolerated dose. Toxicity was clearly related to dose with increasing frequency and severity of

rash, fatigue, and arthralgia at the highest doses. Efficacy was first clearly demonstrated at doses that produced drug exposure that was commensurate with that required to achieve tumor regression of *V600E*BRAF melanoma xenografts preclinically. Objective responses were observed in the vast majority of patients & FDG-PET scans revealed metabolic changes as early as two weeks into therapy. Selected patients underwent biopsy of superficial tumors for the purposes of confirming downregulation of Erk activation and Ki67. Updated data from the phase I/II trial will be presented. As single-agent trials are underway with the aim of establishing single-agent BRAF inhibition as a new standard of care for the BRAF mutated subpopulation, attention now turns to understanding mechanisms of resistance and rational combination approaches.

BRAF targeted therapy provide a new paradigm for matching therapy to somatic genetic changes identified prior to the initiation of therapy. Additional genetic discoveries may provide a basis of combinations of targeted therapy, in an effort to extend the early success of BRAF inhibitors in the subpopulations bearing mutations in this oncogene.

Todd R. Golub, MD

Director of Cancer Program, Broad Institute of Harvard and MIT
Professor, Dana-Farber Cancer Institute

SIGNATURES FOR SMALL MOLECULE DISCOVERY

The application of genomic approaches to the study of cancer holds tremendous promise for improved diagnostic and prognostic tests, and for the elucidation of new therapeutic targets by building a molecular taxonomy of the disease. More recently, we have addressed the challenge of using gene expression data in the drug discovery setting. That is, having defined a gene expression signature of a biological state of interest (e.g. tumor subtype or state of pathway activation), could a small molecule library be screened to identify compounds capable of modulating the signature of interest – and by inference, modulate the biological state under study. We piloted this idea, termed Gene Expression-based High Throughput Screening (GE-HTS), and applied it to the discovery of compounds capable of inducing the myeloid differentiation of acute myeloid leukemia cells. Importantly, the discovery of these compounds did not require a specialized phenotypic assay, nor did it require prior knowledge of the mechanism by which differentiation occurs. We have subsequently applied this GE-HTS concept to the discovery of compounds that inhibit the activity of the Ewing Sarcoma oncogene EWS/FLI and that abrogate androgen receptor signaling in prostate cancer. These experiments establish the feasibility of using a gene expression signature as the read-out of a primary small-molecule screen. Extending on this concept of signature-based chemical screening, we have recently established the feasibility of using a database of gene expression profiles to systematically connect signatures of diseases to signatures of

gene product function or signatures of drug action. We refer to this project as the Connectivity Map project. By querying a centrally generated database of gene expression profiles, users can find ‘connectivity’ between a query signature of interest and one or more treatments (perturbagens) in the database. The data and tools are available at www.broadinstitute.org/cmap and we have used the method to discover relevant connections in dexamethasone-resistant childhood leukemia, androgen response in prostate cancer, among many others. These experiments demonstrate the feasibility of the Connectivity Map approach, and suggest the value of creating a larger, more extensive, publicly accessible Connectivity Map database. Toward that goal, we have piloted a low-cost, high throughput approach based on a reduced representation of the transcriptome capable of supporting truly genome-scale data generation.

W. Michael Korn

Associate Professor of Medicine & Co-Director, Center of Molecular Oncology, Helen Dill Family Comprehensive Cancer Center at UCSF

SYSTEMS-BASED APPROACHES TO DEVELOPING RATIONAL COMBINATION THERAPIES FOR CANCER

Aberrant activity of receptor tyrosine kinase signal transduction pathways in cancer cells results in a multitude of cellular effects critical for development and maintenance of the malignant phenotype. It has become clear that these pathways are complex dynamic molecular networks, characterized by feedback and feed-forward mechanisms. These non-canonical network connections can counteract effects of pharmacological signal transduction inhibitors. In agreement with this, increasing evidence suggests that inhibition of multiple critical pathway nodes is crucial for preventing such cellular escape mechanisms. We are utilizing systems-level assessments of network behavior following inhibition of signal transduction molecules to uncover therapeutically relevant network connections. Resulting datasets are used to create Bayesian network inference and dynamic models. These allow for in silico predictions of new therapeutic targets and optimized treatment schedules.

Tarjei S. Mikkelsen, PhD

Post Doctoral Associate, Broad Institute

COMPARATIVE EPIGENOMIC ANALYSIS OF CELLULAR DIFFERENTIATION

We describe lessons from the generation and comparative analysis of genome-wide chromatin state maps from human and murine models of adipogenesis. The maps provide unprecedented views of chromatin remodeling during cellular differentiation, and allow identification of large numbers of pre-adipocyte and adipocyte-specific regulatory elements based on characteristic chromatin signatures. We find that the specific locations of most such regulatory elements differ between the two models, including at orthologous loci with similar expression patterns. Based on PPARG localization maps, reporter assays and sequence analysis, we show that these differences are determined in part by extensive evolutionary turnover of transcription factor recognition motifs in the genome sequences, and that this turnover may be facilitated by the presence of redundant regulatory elements at differentiation-dependent loci. We also describe how integrated analysis of chromatin state and genome sequences allowed us to predict and validate novel transcription factors in the adipogenic gene regulatory network.

Vamsi Mootha, MD

Associate Professor, HMS Department of Systems Biology, MGH Center for Human Genetic Research, Broad Institute

FROM MITOCHONDRIAL PARTS AND PATHWAYS TO PATHOGENESIS

In this talk I will present our recent efforts to define the mitochondrial proteome, use computational and experimental genomics to define the function of these proteins, and finally, our more recent efforts to use next-generation sequencing to solve the molecular basis of inborn errors of mitochondrial disease. Our work is leading to a mechanistic understanding of the largest class of inborn errors of metabolism, and is helping to motivate new therapeutic strategies.

Eric Perakslis, PhD

Vice President, R&D Informatics Center of Excellence and COSAT, Johnson & Johnson Pharmaceuticals Research and Development

E-HEALTH FROM THE GROUND UP: THE BUILDING OF THE KING HUSSEIN INSTITUTE FOR BIOTECHNOLOGY AND CANCER IN AMMAN, JORDAN

The King Hussein Institute for Biotechnology and Cancer is a \$350 MM effort to construct a new 260-bed hospital and biotechnology research center in Amman, Jordan. KHIBC will be a village of healing and scientific discovery and the first such center in the Arab world. To optimize the technology infrastructure of this green field opportunity, all technology from medical equipment through the IT infrastructure is being engineered by a single team of engineers, scientists and informatics experts.

Sridhar Ramaswamy, MD

Assistant Professor of Medicine, Massachusetts General Hospital Cancer Center; Harvard Medical School; Broad Institute, Harvard Stem Cell Institute

SPONTANEOUS CANCER CELL QUIESCENCE: A NEW PARADIGM

Cancer cell dormancy and drug resistance is a major cause of treatment failure in clinical oncology, but its molecular basis is poorly understood mainly due to a lack of suitable model systems. Our recent studies point to a potentially new system for understanding how highly proliferative, aneuploid cancer cells become dormant in cancer patients.

Aviv Regev, PhD

Early Career Scientist, HHMI; Core Member, Broad Institute; Assistant Professor of Biology, MIT

UNBIASED RECONSTRUCTION OF MAMMALIAN REGULATORY NETWORKS

Deciphering the regulatory networks that control dynamic and specific gene expression responses in mammalian cells remains a major challenge. While models inferred from genomic data have identified candidate regulatory mechanisms, such models remain largely unvalidated. Here, we present an unbiased strategy based on systematic gene perturbation and innovative multiplex detection to derive regulatory networks in mammalian cells. We first apply this approach to decipher the network that controls the transcriptional response to pathogens in primary dendritic cells (DCs), testing the regulatory function of over a hundred transcription factors, chromatin modifiers, and RNA binding proteins. Our approach accurately assigned dozens of known regulators (e.g. NF κ B, IRFs, and STATs) to their target genes and discovered dozens additional functional regulators that were not previously implicated in this response, and quantifies the contribution of each regulator to two major transcriptional programs. We identify a core network of key regulators and fine-tuners that uses a combination of coherent feed-forward circuits, dominant activation, and cross-inhibition to control response specificity. Among these we discover a tier of chromatin modifiers that specifically repress interferon beta 1 (IFN β 1) expression upon bacterial but not viral stimulation, and a large circuit of cell cycle regulators that was co-opted to regulate the viral response. We then show how a similar strategy can be used to study the global architecture of gene regulation across \sim 40 cell populations in human hematopoiesis, from hematopoietic stem cells, through multiple progenitor and intermediate maturation states, to terminally differentiated cell type, implicating dozens of new regulators in hematopoiesis and demonstrate a substantial re-use of gene modules and their regulatory programs in distinct lineages. Our work establishes a broadly-applicable, comprehensive and unbiased approach to identifying the wiring and function of a regulatory network controlling a major transcriptional response in primary mammalian cells.

Eric E. Schadt, PhD

Chief Scientific Officer, Pacific Biosciences, Inc.

MOVING TOWARDS AN UNDERSTANDING OF THE MOLECULAR NETWORKS UNDERLYING BIOLOGICAL HYDROGEN PRODUCTION BY BACTERIA

Environmental concerns over the use of fossil fuels and their role in climate change have sparked research on the development of alternative fuels. Hydrogen is a clean burning alternative fuel that can be produced in large amounts by some bacteria. We have embarked on a systems level approach to dissect metabolic and regulatory networks necessary for nitrogenase-catalyzed hydrogen production by the bacterium *Rhodospseudomonas*. *Rhodospseudomonas* is an ideal platform to develop as a biocatalyst because it is an extremely versatile microbe that produces copious amounts of hydrogen gas by drawing on abundant natural resources of sunlight and biomass. Hydrogen production requires the integration of dozens of metabolic reactions carried out in the context of a complex network of molecular interactions. To identify key drivers for hydrogen production we employed an integrative genomics approach similar to that used with great success to elucidate the causes of common human diseases. We have sequenced the complete genomes and transcriptomes of approximately 100 independently isolated *Rhodospseudomonas* strains. In contrast to mammalian systems, the genomes of these strains are quite different from each other and so a completely accurate genome assembly is required for each strain in order to leverage DNA variation as a systematic source of perturbations for network reconstruction. A breakthrough for this project is the first de novo assembly of bacterial genomes using reads from Pacific Biosciences' single-molecule real-time (SMRT™) DNA sequencing platform using a novel assembly pipeline tailored to SMRT sequencing. This combined with transcriptomic and phenotypic data from 100 strains grown under three different conditions enabled the construction of whole genome, causal gene networks using Bayesian network reconstruction methods, resulting in the identification of subnetworks supported as causal for hydrogen production and nitrogenase activity. Directed perturbations of these networks provide a path to enhance hydrogen production.

Peter Sorger, PhD

Professor of Systems Biology, Harvard Medical School; Professor of Biological Engineering, MIT

PHOSPHODYNAMICS OF RECEPTOR TYROSINE KINASE SIGNALING

The four receptors of the epidermal growth factor receptor (ErbB) family are prototypical receptor tyrosine kinases involved in regulating cell proliferation, motility and differentiation. Mutation or over-expression of ErbB receptors is associated with a wide variety of human cancers and multiple therapeutic antibodies and small molecule kinase inhibitors targeting ErbB1-3 are currently in the clinic or in development. Nonetheless, the mechanisms that determine the magnitude, duration and selectivity of ErbB signaling in normal and transformed cells remain poorly understood. We have undertaken a biochemical study of ErbB1 phospho-dynamics in cultured cells and analyzed the resulting data using a series of mass-action models formalized as networks of ordinary differential equations. These models encompass different aspects of the known or proposed biochemistry of signal transduction at varying levels of molecular detail and, in conjunction with quantitative biochemical data, reveal unexpectedly high rates of phospho-turnover. Whereas existing models suggest one or two receptor phosphorylation-dephosphorylation events during a typical 30-60 min immediate-early ligand response, we find that the number likely exceeds 50,000. We discuss these results with respect to the biology of ErbB-mediated signal transduction, the mechanisms of action of different anti-ErbB drugs and the use of mathematical models to infer normally unobservable aspects of intracellular biochemistry.

Stephen Turner, PhD

Founder and Chief Technology Officer, Pacific Biosciences

REAL TIME DNA SEQUENCING FROM SINGLE POLYMERASE MOLECULES

SMRT (single molecule real time) DNA sequencing is a high-throughput method for eavesdropping on template-directed synthesis by DNA polymerase in real time. Pacific Biosciences has developed two critical technology components which enable this process: The first is phospholinked nucleotides where, in contrast to other sequencing approaches, the fluorescent label is attached to the terminal phosphate rather than the base. The enzyme cleaves away the fluorophore as part of the incorporation process, leaving behind completely natural double-stranded DNA. The second critical component is zero-mode waveguide (ZMW) confinement technology that allows single-molecule detection at concentrations of

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labeled nucleotides relevant to the enzyme. Through the combination of these innovations, our technology allows the speed, processivity, efficiency and fidelity of the enzyme to be exploited. We apply this technology to shotgun sequencing using a fast and simple sample preparation concept that facilitates whole-genome sequencing directly from genomic DNA. supported as causal for hydrogen production and nitrogenase activity. Directed perturbations of these networks provide a path to enhance hydrogen production.

Marc Vidal, PhD

Professor of Genetics, Harvard Medical School
Director, Center for Cancer Systems Biology (CCSB)

INTERACTOME NETWORKS AND HUMAN DISEASE

For over half a century it has been conjectured that macromolecules form complex networks of functionally interacting components, and that the molecular mechanisms underlying most biological processes correspond to particular steady states adopted by such cellular networks. However, until recently, systems-level theoretical conjectures remained largely unappreciated, mainly because of lack of supporting experimental data. To generate the information necessary to eventually address how complex cellular networks relate to biology, we initiated, at the scale of the whole proteome, an integrated approach for modeling protein-protein interaction or “interactome” networks. Our main questions are: How are interactome networks organized at the scale of the whole cell? How can we uncover local and global features underlying this organization, and how are interactome networks modified in human disease, such as cancer?

Robert Weinberg, PhD

Member, Whitehead Institute
Professor of Biology, MIT

MALIGNANT PROGRESSION AND THE STEM CELL STATE

A variety of lines of evidence now converge on the conclusion that passage through an epithelial-mesenchymal transition (EMT) confers on epithelial cells not only the attributes of mesenchymal cells, but also many of the properties of epithelial stem cells. This holds true for both normal and neoplastic human mammary cells, but the applicability of this for non-mammary cells remains to be demonstrated. Entrance into the stem-cell state confers on neoplastic cells the ability to seed new tumors, leading to

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the notion that cancer stem cells are cells that have passed through an EMT. Targeting CSCs through directed agents is an important issue in the development of novel chemotherapeutics. However, the eradication of the CSCs, if possible, may not, on its own, yield durable clinical responses because of the plasticity of stem cells and non-stem cells within tumors.