2nd Epigenetics in Drug Discovery

PLENARY KEYNOTE SPEAKERS
George Church, Ph.D.
Professor of Genetics, Director of the Center for
Computational Genetics
Harvard Medical School

Craig C. Mello, Ph.D.
Nobel Laureate
Blais Professor, Molecular Medicine
University of Massachusetts Medical School
Howard Hughes Investigator
HHMI

G. Steven Burrell
Chief Executive Officer
Burrell & Company

KEYNOTE SPEAKER
Alexander Meissner, Ph.D.
Assistant Professor
Harvard University
Senior Associate Member
the Broad Institute of MIT and Harvard

FEATURED SPEAKER
Arthur M. Krieg, M.D.
Chief Executive Officer
RaNA Therapeutics

FEATURED SPEAKER
Rab Prinjha
Interim Head of Epinova Epigenetics DPU,
Head of Biology
GlaxoSmithKline, UK

A Track of the Omics Evolution Summit

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2nd Genomic & Proteomic Drug Discovery
3rd RNAi Research & Therapeutics
7th Protein Kinases in Drug Discovery
2nd Next Generation Sequencing
Genome-wide Partnering and Deal-Making

Attend the Pre-Summit Workshop on May 29th, 2012
Clinical Sequencing Workshop

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FEATURED PRESENTATION

8:05 DNA Methylation Dynamics in Development and Stem Cells

Alexander Meissner, Ph.D., Assistant Professor, *Harvard University*; Senior Associate Member, *the Broad Institute of MIT and Harvard*

Cytosine methylation in mammals is an epigenetic modification that is largely restricted to CpG dinucleotides and serves multiple critical functions including stable repression of target promoters, maintaining genomic integrity, establishing parent-specific imprinting patterns, and silencing endogenous retrotransposon activity. In somatic tissues, CpG methylation exhibits global patterns based on relative CpG density: it is unmethylated in localized CpG islands at housekeeping or developmental promoters, and hypermethylated at non-regulatory CpGs distributed elsewhere in the genome. This landscape is relatively static across all somatic tissues that have been examined to date on a genome scale, where the majority of methylated CpGs are pre-established and inherited through cell divisions. Generally, only a small fraction of CpGs switch their methylation levels as part of an orchestrated regulatory event. By contrast, DNA methylation is much more dynamic during mouse germ-cell and pre-implantation development. I will present recent insights gained through genome-scale mapping of DNA methylation in human pluripotent stem cells and murine development.

8:40 Discovery of a Novel Epigenetic Methylation Mark Catalyzed by SET and MYND Domain Containing Protein 3 (Smyd3)

Olena Barbash, Investigator, Cancer Epigenetics DPU, *GlaxoSmithKline*

9:05 Redox-sensitive Epigenetic Regulation: Implications for Brain Disorders, Addiction and Development

Richard Deth, Ph.D., Professor, Pharmacology, *Northeastern University*

More than 200 methylation reactions, including global DNA and histone methylation, are dependent upon the SAM/SAH ratio, which is in turn dependent upon activity of methionine synthase (MS). The cobalamin cofactor of MS renders it highly sensitive to cellular redox status, providing an avenue for epigenetic regulation by factors promoting either oxidative stress or increased synthesis of the antioxidant glutathione. Unique redox features of human brain have evolved to optimize this mode of epigenetic regulation, and a number of brain disorders occurring throughout the lifespan reflect its dysfunction. For example, disruption during early development can lead to autism, while impaired methylation late in life is associated with Alzheimer’s disease. In addition, recent evidence indicates an important role for epigenetics in drug addiction. Since epigenetic regulation is at least partially amenable to metabolic modulation, opportunities exist to therapeutically impact neurodevelopmental, neuropsychiatric and neurodegenerative disorders. Moreover, recognition of redox-sensitive epigenetic regulation provides a useful perspective for understanding the physiological control of gene expression during development and adaptive responses associated with successful aging.

This talk will provide the following “benefits”:
- An understanding of global DNA and histone methylation regulation
- A familiarity with the metabolic pathways regulating cellular redox status
- An appreciation of human brain-specific redox and methylation regulation
- An awareness of age-dependent and disease-dependent changes in methylation status
- An understanding of potential treatment approaches

9:30 An Epigenetic Blockade of Cognitive Functions in the Neurodegenerating Brain

Johannes Graeff, Ph.D., *Brain and Cognitive Neurosciences, Li-Huei Tsai’s Lab, The Picower Institute for Learning and Memory, Massachusetts Institute of Technology*

9:55 Networking & Refreshment Break
chromatin from postmortem PFC across the lifespan and map the genome-wide distribution of histone H3-trimethyl-lysine 4 (H3K4me3), an epigenetic mark associated with transcriptional regulation.

Methods: Neuronal nuclei from postmortem prefrontal cortex were immunotagged with NeuN antibody, and NeuN+ and NeuN- nuclei sorted separately via fluorescence-activated nuclei sorting, and purified mononucleosomes enriched for H3K4me3 analyzed by massively parallel sequencing. Neuronal H3K4me3 epigenomes were obtained from the PFC of control subjects from late prenatal to old age, and compared to epigenomes of subjects on the autism or schizophrenia spectrum.

Results: We present evidence for a highly regulated, ‘pre-programmed’ remodeling of histone methylation landscapes in immature PFC neurons that lasts at least into the early childhood years, involving hundreds of loci and a distinct set of transcription factors. Furthermore, histone methylation alterations in prefrontal neurons of diseased subjects were highly variable. As a group, loci with disease-associated H3K4me3 alterations showed a significant, 2-3 fold enrichment for genes associated with heritable risk for neurodevelopmental disease. We estimate that less than 5% of altogether 711 loci affected in our cohort of 16 autism subjects were related to a copy number variant at that site. Taken together, these findings highlight the ‘epigenetic vulnerability’ of the immature PFC and point to significant overlap between the genetic and epigenetic risk architectures of major psychiatric disease.

Acknowledgements: We thank Dr. Ron Zielke and staff from Brain and Tissue Bank of the University of Maryland, Dr. Francine M. Benes and staff from the Harvard Brain Tissue Resource Center and the Autism Tissue Program (Director; Dr Jane Pickett), and Dr. William E. Bunney Jr. and Dr. Edward G. Jones at the University of California, Irvine and Davis, and Dr. Andree Lessard at the University of Maryland/Maryland Psychiatric Research Center for supplying some of the postmortem brain tissue used in this study, and Dr. Ellen Kittler and Dr. Maria Zapp from the UMMS Deep Sequencing Core and Dr. Richard Konz and staff from the UMMS Flow Cytometry core. The work was supported by Autism Speaks, the International Mental Health Research Organization, the National Alliance for Research on Schizophrenia and Depression, and the National Institute of Mental Health.

11:20 The Complexity of Complex Disease: Schizophrenia
Cassandra Smith, Ph.D., Professor, Biomedical Engineering, Biology and Pharmacology and Experimental Therapeutics, Director, Molecular Biotechnology Research Laboratory, Boston University

11:45 SWI/SNF Complexes: Chromatin, Epigenetics and Cancer

Charles W. M. Roberts, M.D., Ph.D., Associate Professor, Pediatric Oncology, Dana-Farber Cancer Institute, Children’s Hospital and Harvard Medical School
SWI/SNF chromatin remodeling complexes utilize the energy of ATP hydrolysis to remodel nucleosomes and modulate transcription. Growing evidence indicates that these complexes serve a widespread role in tumor suppression as frequent inactivating mutations in multiple SWI/SNF subunits have recently been identified in a variety of cancers, including those of ovary, kidney, lung, liver, stomach, bladder, colon, breast and pancreas. My laboratory studies the SWI/SNF complex using mouse models, cell lines and primary human tumor samples. Insights into the normal function of these complexes, the mechanisms by which mutations drive cancer formation, and opportunities for therapeutic intervention will be discussed.

12:10 Lunch On Your Own

1:40 Targeting Novel Epigenetic Regulators for Treatment of Hematopoietic Tumors and Inflammation
Hozefa Bandukwala, Instructor, Signaling and Gene Expression, La Jolla Institute of Allergy and Immunology

2:05 Siruins in Epigenetic Control and Disease Processes
David Sinclair, Ph.D., Professor, Genetics, Harvard Medical School

Sirtuins are a family of NAD+-dependent deacetylases implicated in mediating the health benefits of calorie restriction and possibly exercise. What roles these enzymes play in human health and whether or not they can be safely targeted by drugs remains an open question. My talk will focus on recent developments in the sirtuin field in understanding both the biology and in drug development, including a mechanistic understanding of how sirtuins can be directly activated by small molecules.

Benefits:
1. Learn about new roles for sirtuins in human disease
2. Learn about a new and simple assay for sirtuin activity
3. Hear about new possible causes of aging involving epigenetic changes
4. Discuss whether it is possible to activate chromatin modifying proteins allosterically

2:30 Peng Jin, Ph.D., Associate Professor, Human Genetics, Emory University School of Medicine

2:55 [Oral Presentation from Exemplary Submitted Abstracts]
To be considered for an oral presentation, please submit an abstract here by April 30.

3:25 Networking & Refreshment Break
Recent studies have revealed that most of the genome is transcribed into non-coding RNA. A major category of this is long non-coding RNA (lncRNA), which in some cases can regulate gene expression in either a cis or trans fashion. One of the mechanisms through which lncRNA regulate gene expression is through recruitment of PRC2. On the X chromosome, PRC2 recruitment to the lncRNA Xist operates in cis to suppress gene expression, resulting in selective X chromosome inactivation. Oligonucleotide complementary to Xist can prevent the binding of PRC2 or other specific epigenetic factors, thereby interfering with X chromosome inactivation. We present evidence that this or a similar mechanism may operate much more generally across the genome to constitutively suppress transcription, and that oligonucleotide inhibitors of lncRNA interactions with epigenetic factors such as PRC2 may selectively de-repress gene expression in vitro and in vivo. The selective induction of gene expression could have dramatic therapeutic benefits in many disease settings.

Huntington's disease (HD) is neurodegenerative genetic disorder that affects muscle coordination and leads to cognitive decline and psychiatric problems. The disease is caused by an autosomal dominant mutation in the Huntingtin protein (Htt) in the form of an expansion of CAG repeats. Wild type Htt (indirectly) interacts with REST/NRSF, a protein that controls the expression of many neuron specific genes, to retain REST/NRSF in the cytoplasm. The mutated htt protein is less efficient and as a consequence, REST/NRSF was reported to pathologically enter the nucleus of affected cells and to bind to its target RE1/NRSE sites. REST then draws repressive chromatin modifying complexes comprising CoREST, HDAC1/2 and LSD1 to its target sequences, silencing genes like BDNF. Our central hypothesis for HD was that we could disrupt REST containing complexes by inhibiting the function of its essential components, including LSD1.

Monoamine oxidase B (MAOB) is a flavin-dependent enzyme structurally related to LSD1 and a therapeutic target for the treatment of neurological disorders. Abnormally high levels of monoamine oxidase (MAO-B) activity have been identified in the human HD brain, and there is mounting evidence that the metabolism of the transmitter dopamine by the MAO enzymes may contribute to striatal damage in mitochondrial toxin-induced models of HD.

Here we report the development of novel specific LSD1 and dual LSD1/MAOB inhibitors for the treatment of Huntington's Disease and the selection of a candidate for development. Oryzon’s drug candidate is a compound with a low MW, good pharmacological properties, orally bioavailable, good BBB crossing properties and safety and selectivity profile.

Much of the mammalian genome is transcribed into noncoding RNAs of different categories. This lecture will primarily be concerned with natural antisense transcripts (NATs) most of which are long noncoding RNAs. NATs are found in most gene loci and regulate gene expression through several distinct mechanisms including chromatin modifications. Inhibition/perturbation of endogenous NATs by modified oligonucleotides called AntagoNATs, in vitro or in vivo, reveals concordant or discordant regulation and results in down- or up-regulation of conventional (protein-coding) gene expression, respectively. Evidence will be presented that AntagoNATs can potently induce locus-specific and reversible modulation of gene expression associated with alterations in chromatin marks.
Thursday, May 31, 2012

Plenary Keynote Session
Moderator: Shidong Jia, Scientist, Genentech

KEYNOTE PRESENTATION

8:00  Innovating in the New Austerity: What’s Really Happening and Why Creative Dealmaking is Essential

Steven Burrill, Chief Executive Officer, Burrill & Company

Pharmaceutical R&D spending is falling, the demand for innovation is increasing, and the traditional business model for the industry is failing. What does innovation look like today in the new austerity and what will it take to be successful? What’s required is creativity in raising money, making deals, and forging new business models. Burrill brings his 45 years of successful dealmaking, company building, and investing to this discussion.

KEYNOTE PRESENTATION

8:45  The Personal Genome Project - Open Access to Genome Sequences + Trait data.

George Church, Ph.D., Professor, Genetics; Director, Center for Computational Genetics, Harvard Medical School

The PGP enables open observation and critique of a large cohort “test-driving” comprehensive participatory personalized medicine. Since 2004, we have helped push down the cost of reading and writing DNA (and biological systems) down by a million-fold (5-fold faster exponential than Moore’s law) and enabled fully open-access human Genome+Environment=Trait (GET) data, stem cells, and clinical community curation/interpretation tools (Evidence.PersonalGenomes.org). This involves inherited genomes plus day-to-day genomic variation -- cancers, microbes, allergens, vaccines, & subcellular-resolution epigenomics. We are also sequencing centenarians and long-lived mammals. Benefits include human genome engineering technologies for personalized diagnostics as well as stem cell, synthetic organ, microbiome and immunome transplantation therapies.

KEYNOTE PRESENTATION

9:30  RNAi and Immortality: Recognition of Self/non-Self Nucleic Acids

Craig C Mello, Ph.D., Nobel Laureate, Blais Professor in Molecular Medicine, University of Massachusetts Medical School; Howard Hughes Investigator, HHMI

Organisms exhibit a fascinating array of gene-silencing pathways, which have evolved, in part, to confront invasive nucleic acids such as transposons and viruses. Not surprisingly, these pathways are highly active in the germline and can be elicited upon the introduction of transgenes. A key question raised by the existence of these pathways is how do they distinguish self- from non-self nucleic acids? Evidence exists for a number of cues that might facilitate the recognition of foreign sequences including, copy-number sensing, sensing of unpaired DNA, or the sensing of aberrant RNA (e.g. dsRNA). Here we report on a remarkable silencing pathway that can permanently silence even single-copy transgenes. We show that the initiation of silencing depends on the piwi Argonaute PRG-1 and its genomically encoded piRNA cofactors. Our findings support a model in which PRG-1 scans for foreign sequences while two other Argonaute pathways serve as epigenetic memories of “self” and “non-self” RNAs. These findings suggest that organisms utilize RNAi-related mechanisms to keep inventory of all genes expressed in the germ-line, and to recognize and silence foreign genes.

10:15  Networking & Refreshment Break

Enabling Diagnostics and Technologies for Epigenetics Drug Discovery
Moderator: Hella Kohlhof, Ph.D., Manager, 4SC AG

10:45  High-throughput TR-FRET Cellular Assays for Interrogating Posttranslational Modifications of p53 and Histone H3

Kun Bi, Ph.D., Senior Staff Scientist, Primary and Stem Cell Systems, Life Technologies

Post-translational modifications such as phosphorylation, acetylation and methylation play important roles in regulating the structures and functions of histones, which in turn regulate gene expression and DNA repair and replication. Histone modifying enzymes, such as deacetylases, methyltransferases and demethylases, have been pursued as therapeutic targets for various diseases. However, detection of the activities of these enzymes in high-throughput cell-based formats has remained challenging. We have developed high-throughput LanthaScreen® cellular assays for histone H3 and p53 site-specific modifications. These assays utilize cells expressing green fluorescence protein (GFP) tagged-histone H3 (or p53) transiently delivered via BacMam and terbium labeled-anti-histone H3 (or p53) modification-specific antibodies. Robust time-resolved Förster resonance energy transfer signals were detected for H3 lysine-9 acetylation and dimethylation (H3K9me2), serine-10 phosphorylation, K4 di- and tri-methylation and K27 tri-methylation. Consistent with previous reports, methyltransferase G9a inhibitor UNC-0638 decreased K9me2 levels significantly with little effects on other modifications. Further validation of these assays using methyltransferases-specific RNAi oligos demonstrated that EZH2-specific RNAi reduced the level of K27me3 with little effect on the other three modifications, whereas G9a RNAi and SMYD3 RNAi reduced K9me2 and K4me2/3, respectively. To demonstrate the utility of this
11:10 Integrative Biomarker Study in Colon Cancer

Shidong Jia, Scientist, Oncology Biomarker Development Group, Genentech

Dr. Jia’s lab has developed working procedures to evaluate FFPE-based microRNA and epigenetic signature as biomarker for cancer prognosis, prediction and patient stratification. In particular, their work have refreshed current practice and demonstrated new approach for studying microRNA and epigenetic profiling in FFPE samples.

11:35 Chemical Probes for Epigenetics

Dafydd Owen, Ph.D., Associate Research Fellow, Pfizer

Chemical modifications of histones that influence epigenetic regulation include changes such as methylation of lysine/arginine residues and acetylation of lysine residues. A number of epigenetic enzymes have now been identified that either introduce these epigenetic marks (‘writers’) or remove them (‘erasers’). In addition, regulatory proteins have been discovered that directly recognize histone modification status (‘readers’) and drive the localisation of complexes which control gene expression. Research into the role of epigenetics in disease could be significantly accelerated if chemical probes for such targets were available that were suitable for cell-based studies.

Pfizer is a member of a public-private partnership led by the Structural Genomics Consortium (SGC) to help identify a suite of high-quality chemical probes for epigenetic targets. This partnership is unique in that it brings the medicinal chemistry expertise within industry together with biological expertise in academia to drive basic research in an emerging area of important biology. This presentation will describe recent progress in this collaboration and highlight the discovery of novel chemical probes for epigenetic proteins that may have an important role in disease.

Benefits:
1. The discovery story of chemical probes for Bromodomains and Methyltransferases
2. Full biological profile of a second generation BET inhibitor
3. The case for pre-competitive chemical probes
4. The Structural Genomics Consortium

12:00 Oral Presentation from Exemplary Submitted Abstracts

To be considered for an oral presentation, please submit an abstract here by April 30.

12:25 Lunch Provided by GTC
2:45 SGI-110, a Novel Subcutaneous Second Generation Hypomethylating Agent

Tom Heightman, Director, Medicinal Chemistry, Astex Pharmaceuticals

SGI-110 is a novel second generation DNA methylation inhibitor that is currently in Phase I/II clinical study for treatment of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). SGI-110 is a dinucleotide prodrug of decitabine designed to be less prone to deamination by cytidine deaminase. Potential advantages over decitabine include improved stability, reduced toxicity and a more convenient and less frequent subcutaneous administration.

In this talk we will present the latest preclinical and clinical findings of SGI-110. In non-human primates, subcutaneous SGI-110 in either weekly×3 or daily×5 regimens achieved DNA hypomethylating effects that were similar to or better than with decitabine IV, at a lower dose and with less myelosuppressive effects.

In clinical studies to date SGI-110 dosed subcutaneously is safe and well tolerated. Blood levels of decitabine are obtained that are biologically effective and are in the range that produces a therapeutic response to IV decitabine. These levels have been achieved with little toxicity so far. The PK profiles show efficient conversion of SGI-110 to decitabine with achievable therapeutic exposures, longer apparent half life, and lower Cmax than predicted equivalent decitabine doses given IV. Global hypomethylating effects have been observed at all dose levels evaluated to date, and preliminary efficacy (PR+CR) has been observed in relapsed AML subjects.

3:10 Epigenetic Strategies to Target Advanced Breast Cancer

Peter Ordentlich, Ph.D., Vice President, Translational Medicine, Syndax Pharmaceuticals

3:40 Conference Concludes
Registration Form

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