

MEETING OBJECTIVES

To bring together experts in epigenetics from academia and industry to discuss the application and future directions of this field to oncology research and therapeutics and more specifically to:

- Discuss the overall progress that has been made to understand the importance of epigenetics in myeloma biology and the treatment of the disease
- Identify the gaps and critical issues that need to be addressed in order to increase knowledge of epigenetic regulation in myeloma
- Develop a program project RFA in Epigenetics and Myeloma

AGENDA

Wednesday, March 16

7:00 PM

Dinner and Keynote Speaker

Epigenetics Therapeutics for the Treatment of Cancer – Where the Field Stands and Future Directions

Victoria M. Richon, PhD

Epizyme, Inc.

Thursday, March 17

7:00 AM

Breakfast and Registration

8:00

Welcome and Introductions

Joan Levy, PhD

Multiple Myeloma Research Foundation

8:05

Introduction and Meeting Objectives

John Carpten, PhD

The Translational Genomics Research Institute

8:15

Multiple Myeloma: An Overview of the Biology and Treatment

James Bradner, MD

Dana-Farber Cancer Institute

Harvard Medical School

8:45

Integrative Modeling of Transcription Factor Binding, Epigenetic Marks, and Gene Expression Reveals Mechanisms of Gene Regulation in Lymphoma Cells

Olivier Elemento, PhD

Weill Cornell Medical College

9:15 AM

Comprehensive and High-Throughput DNA Methylation Analysis of Human Cancers

Dan Weisenberger, PhD

University of Southern California Epigenome Center

AGENDA

Thursday, March 17

- 9:45 AM **Break**
- 10:00 **The Importance of Epigenetics in Myeloma and Related Disorders**
- **Epigenetic Findings Learned From Genomics**
Jonathan Keats, PhD
The Translational Genomics Research Institute
 - **DNA Methylation in Myeloma**
Bodour Salhia, PhD
The Translational Genomics Research Institute
 - **MMSET and HMTs**
Jonathan Licht, MD
Northwestern University
 - **microRNA Aberrations Modulate Waldenström's Macroglobulinemia Biology**
Aldo Roccaro, MD, PhD
Dana-Farber Cancer Institute
- 11:30 **Working Lunch and Working Sessions**
- Goal: To identify gaps and critical needs to further understand the role of epigenetics in myeloma in order to identify new targets, therapeutics, and potential biomarkers
- **Epigenetic Modifications Leading to a Better Understanding of the Disease and Treatment**
 - **Genomic Findings/Epigenetic Target Validation**
 - **Lead Development and Testing/Preclinical Assays, Model, and Technology Development**
- 1:30 PM **Break**
- 1:45 **Action Planning for Development of Program Project RFA in Epigenetics and Myeloma**
Working Session Chairs
- 3:00 **Next Steps and Wrap-Up**
- 3:30 PM **Adjournment**

BIOGRAPHIES – FACULTY**James Bradner, MD**

*Harvard Medical School
Dana-Farber Cancer Institute*

Dr. Bradner is a physician-scientist exploring the interface between chemical biology and molecular oncology. Presently, he is affiliated with the Chemical Biology Program at the Broad Institute of Harvard and MIT and the Division of Hematologic Neoplasia at the Dana-Farber Cancer Institute. The primary focus of his laboratory research concerns the identification of selective small molecules antagonizing enzymatic components of chromatin remodeling complexes. In addition, he is using forward chemical genetic approaches to explore protein catabolism in the cancer cell. These approaches require the development of novel, high-throughput screening techniques and the use of structure-activity relationship models informing the synthesis of focused chemical libraries. The primary focus of his clinical work is the early-phase development of targeted strategies in hematology. He is a staff physician at the Dana-Farber Cancer Institute and attends on the allogeneic stem cell transplantation service.

John Carpten, PhD

The Translational Genomics Research Institute

Dr. Carpten earned his PhD in Molecular, Cellular, and Developmental Biology at The Ohio State University in 1994 with a focus on human genome physical mapping and positional candidate cloning. He then went on to complete a postdoctoral fellowship at the National Human Genome Research Institute, NIH, Bethesda, MD, in Cancer Genetics, where he was later promoted to the tenure track in 2000. Dr. Carpten then accepted a position to become Division Director at The Translational Genomics Research Institute (TGen), Phoenix, AZ, in 2003 where he currently directs the Division of Integrated Cancer Genomics.

Dr. Carpten's research program centers around the development and application of cutting-edge molecular technologies and bioinformatics analysis in search of germ-line and somatic alterations that are associated with risk and tumor characteristics, respectively. He has led and co-authored a series of articles describing the roles of both low and high penetrant genetic variants in cancer risk in *Science*, *Nature Genetics*, *Genome Research*, the *Journal of the National Cancer Institute*, and *The New England Journal of Medicine*.

Dr. Carpten also has a very active program in sporadic tumor research. His laboratory participated in and led several high impact studies including the identification of NF- κ B pathway mutations in multiple myeloma, which was published in *Cancer Cell* in 2007. He also led a landmark study, which culminated in the discovery of the AKT1(E17K) activating mutation in human cancers, published in *Nature* in 2007.

To improve and speed up the discovery of important alterations associated with cancer, Dr. Carpten is co-leading the implementation, development, and application of Next Generation Sequencing (NGS) technologies at TGen. These technologies offer the opportunity to sequence entire cancer genomes to aid in discovery of mutations, copy number changes, and rearrangements such as translocations. Currently, the largest efforts of the Carpten laboratory are in applying NGS for Genomics Enabled Medicine, where cancer genomes and transcriptomes are sequenced and used to identify actionable targets for selective therapeutics. It is his hope that this work will one day lead to improvements in knowledge-based therapeutics toward the reduction in deaths due to cancer.

BIOGRAPHIES – FACULTY (CONT)**Olivier Elemento, PhD***Weill Cornell Medical College*

Dr. Elemento is an assistant professor at the Institute for Computational Biomedicine and Department of Physiology and Biophysics at Weill Cornell Medical College in NY. The focus of Dr. Elemento's group is on cancer systems biology in which they are trying to elucidate the patterns of aberrant pathway activities, rewiring of regulatory networks, and cancer mutations that have occurred in cancer cells. His group uses high-throughput sequencing (ChIP-seq, RNA-seq, bisulfite conversion followed by sequencing, exome capture, and sequencing) to decipher epigenetic mechanisms and regulatory networks at play in malignant cells and to study how they affect gene expression. His lab has developed several computational approaches for analysis of deep sequencing data (eg, ChIPseeqer [for integrative analysis of ChIP-seq data] and SNVseeqer [full pipeline for mutation detection and characterization from deep sequencing data]). They have developed several additional computational approaches that include a pathway analysis tool (iPAGE) and several tools for regulatory element detection (FIRE and FastCompare). His group is also developing data-integrative modeling approaches that integrate genome-wide epigenetic patterns and transcription factor binding (revealed by ChIP-seq) to predict gene expression in lymphoma cells. Expanding upon previous work (De Renzis, Elemento et al, 2007), they are using computer vision and machine learning tools to quantify gene expression at the single cell level in stained lymphoma slides, in order to provide more accurate lymphoma diagnostics and adjust therapy. This complements ongoing work on the role of EZH2 in lymphoma and on DNA methylation patterns in lymphoma.

Jonathan Keats, PhD*The Translational Genomics Research Institute*

Dr. Keats is an assistant professor at The Translational Genomics Research Institute (TGen) in Phoenix, AZ. Dr. Keats has been actively involved in the myeloma research community for more than 12 years. He has authored more than 21 papers and received 15 awards in recognition of his work. He received his PhD from the University of Alberta in 2005 where he studied the clinical and biological consequences of t(4;14)(p16;q32) multiple myeloma in the laboratory of Dr. Linda Pilarski. These studies establish the clinical significance of t(4;14) in myeloma and the target gene of this event. After completing his PhD studies, he moved to the Mayo Clinic for his postgraduate training. At the Mayo Clinic, he worked with Dr. Leif Bergsagel to identify novel genetic events underlying the pathogenesis of multiple myeloma. His work using DNA microarrays resulted in the identification of a series of genetic alterations that result in the constitutive activation of the NF- κ B pathway in at least 20% of myeloma patients. He is also highly involved in the ongoing Multiple Myeloma Genomics Initiative that aims to characterize the genetic events underlying this disease. The primary disease focus of his lab is multiple myeloma with secondary interests in other hematological malignancies and immunodeficiency syndromes. His lab uses novel methods to interrogate the genomic features of these diseases with the goal of identifying genetic events that drive the development, progression, or mediate therapeutic resistance.

BIOGRAPHIES – FACULTY (CONT)

Jonathan Licht, MD
Northwestern University

Dr. Licht is the Johanna Dobe Professor of Medicine and Chief of the Division of Hematology/Oncology at the Northwestern University Feinberg School of Medicine.

Dr. Licht's laboratory studies aberrant gene regulation repression as a cause of hematologic malignancy, including acute promyelocytic leukemia, multiple myeloma, and myeloproliferative neoplasms, and developing small molecules and peptides strategies to revert abnormal gene regulation and treat disease.

Dr. Licht has held a Leukemia Society Scholar award and Burroughs Wellcome Clinical Scientist Award in Translational Research. He is currently the Principal Investigator of a Specialized Center of Research Excellence grant from The Leukemia & Lymphoma Society, studying epigenetic mechanisms in hematological malignancy. He is a Senior Editor of *Clinical Cancer Research* and serves on the editorial board of *Oncogene*, *Cancer Biology and Therapy*, and *Clinical Epigenetics*. Dr. Licht was a Councilor of the American Society for Clinical Investigation and is a member of the Association of American Physicians. Dr. Licht currently serves on the National Cancer Institute Board of Scientific Counselors.

Victoria M. Richon, PhD
Epizyme, Inc.

Dr. Richon joined Epizyme, Inc., in October 2008 from the Merck Research Laboratories, Boston, MA, where she was Senior Director of Cancer Biology and Therapeutics.

Prior to Merck, Dr. Richon was a leading member of the scientific group at Memorial Sloan-Kettering Cancer Center (MSKCC) that discovered the histone deacetylase inhibitor vorinostat (SAHA). This discovery was the basis of Aton, a company that Dr. Richon co-founded and for which she served as Executive Director of Biology. Aton was acquired by Merck in 2004 and Dr. Richon continued supporting vorinostat through its approval by the US FDA in October 2006 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL), a form of non-Hodgkin's lymphoma. Marketed under the name Zolinza[®], vorinostat is the first histone deacetylase inhibitor approved for the treatment of cancer.

Dr. Richon has been a participating member of the American Association for Cancer Research (AACR) since 1993 serving on program committees for the AACR annual meeting, AACR special conferences, as well as review committees for AACR fellowships.

Dr. Richon received her BA in Chemistry from the University of Vermont and her PhD in Biochemistry at the University of Nebraska. She completed her postdoctoral research at the MSKCC.

BIOGRAPHIES – FACULTY (CONT)

Aldo Roccaro, MD, PhD

*Dana-Farber Cancer Institute
Harvard Medical School*

Dr. Roccaro is a senior research scientist and research associate in medicine at the Dana-Farber Cancer Institute, Harvard Medical School in Boston, MA. He is the principal investigator of a targeted epigenetic modifications in multiple myeloma study, in which the major goals of the project are the identification of epigenetic changes as key regulators of multiple myeloma pathogenesis.

Dr. Roccaro also researches preclinical validation of small molecules and has been pioneering work on microRNA in Waldenström's Macroglobulinemia and multiple myeloma. Dr. Roccaro plans to continue these exciting studies by using specific microRNA antagonists and mimetics in order to provide the preclinical evidence of using new microRNA-targeted therapies in these diseases.

Bodour Salhia, PhD

The Translational Genomics Research Institute

Dr. Salhia is a postdoctoral fellow under Dr. John Carpten in the Division of Integrated Cancer Genomics at The Translational Genomics Research Institute (TGen) in Phoenix, AZ. Dr. Salhia's research focuses on the identification and characterization of novel molecular targets for the treatment of multiple myeloma, breast cancer, and CNS metastasis using genomic, epigenomic, and cellular molecular approaches.

Dr. Salhia is a co-leader of The TGen Post-Doc Association and an associate member of the American Association of Cancer Research. She has authored or co-authored more than 17 peer-reviewed articles, has been an invited presenter outlining her research, and is an active volunteer for several community outreach programs in the Phoenix area.

Dan Weisenberger, PhD

University of Southern California Epigenome Center

Dr. Weisenberger is an expert in cancer epigenetics and DNA methylation assay technologies. He trained as a postdoctoral researcher under the mentoring of Dr. Peter A. Jones and Dr. Peter W. Laird, both of whom are internationally recognized experts and pioneers in epigenetics. He was the lead author on the report of a strong association between DNA methylation and BRAF mutation in a subset of human colorectal cancer (*Nature Genetics* 2006;38:787) and contributed to the discovery that embryonic stem cell Polycomb repressor targets are predisposed to abnormal DNA methylation in cancer (*Nature Genetics* 2007;39:157). He currently oversees the DNA methylation data production for The Cancer Genome Atlas (TCGA) consortium and contributed to the genome-scale epigenetic analysis of glioblastoma multiforme for TCGA (*Nature* 2008;455:1061). He also serves as a laboratory manager and project manager at the University of Southern California (USC) Epigenome Center and is an expert in DNA methylation assay platforms and technologies. In early 2010, he was appointed as an Assistant Professor of Research in the Department of Biochemistry and Molecular Biology at USC.

BIOGRAPHIES – MMRF/C

Walter Capone, MBA

Multiple Myeloma Research Foundation

Multiple Myeloma Research Consortium

Mr. Capone oversees the core business operations of the Multiple Myeloma Research Foundation (MMRF) and as part of the Executive Committee executes the growth initiatives outlined in the organization's strategic plan. He has 20 years of pharmaceutical and biotechnology leadership experience in the areas of Commercial Development, Operations, Finance, Marketing, and Sales in the United States and internationally. Prior to joining the MMRF, he was the Vice President of Commercial Development and Operations at Progenics Pharmaceuticals. He previously worked at a number of entrepreneurial pharmaceutical and biotechnology ventures throughout the United States and Europe including Trimeris, Triangle Pharmaceuticals, and Cyanamid Benelux. He started his career at leading global pharmaceutical companies including Lederle, Wyeth, and Bristol-Myers Squibb. He received his BA in International Relations from Brown University and he has an MBA in Finance and International Business from Columbia University Business School.

Louise Perkins, PhD

Multiple Myeloma Research Foundation

Dr. Perkins is the Chief Scientific Officer at the MMRF where she is responsible for the strategic development and execution of the MMRF's scientific agenda to accelerate the development of the next treatments for patients with myeloma, leading to a cure. She has been with the MMRF since 2007 and has more than 16 years of pharmaceutical research experience from two major companies.

Dr. Perkins' research interests center on translational research from target identification through early clinical testing. She has led continued expansion of the MMRF-funded Multiple Myeloma Genomics Initiative which sequenced, in its entirety, the first myeloma tumor genome in 2009 and comprehensively analyzed the genomic profiles of 250 myeloma patient samples collected via the Multiple Myeloma Research Consortium's Tissue Bank. In addition, she has propelled the growth of the MMRF's Venture Philanthropy programs including the MMRF Biotech Investment Award and its first Clinical Fund project both of which support the early clinical testing of promising drugs in myeloma patients.

Prior to joining the MMRF, Dr. Perkins was Director of Cancer Research at Bayer Pharmaceuticals Corporation in West Haven, CT, where she contributed to advancing novel targeted therapies toward clinical study, including Nexavar[®] and other innovative signal transduction inhibitors. While at Bayer, she also served as the Director of Research Licensing and was responsible for oncology licensing activities in support of cancer research programs. Prior to joining Bayer, she led a cancer research group at the Schering-Plough Research Institute in Kenilworth, NJ. In this role, she participated in several early-stage research programs including novel target-finding research using human genomics data.

Dr. Perkins graduated from the University of Michigan with a PhD and MS in Biological Chemistry and conducted postdoctoral studies at Princeton University in the Department of Molecular Biology. She earned her BS in Zoology from the University of North Carolina at Chapel Hill.

BIOGRAPHIES – MMRF/C (CONT)

Joan Levy, PhD

Multiple Myeloma Research Foundation

Dr. Levy is Associate Director of Research at the MMRF where she is responsible for the planning and implementation of the MMRF's research agenda. She has more than 20 years of experience in oncology and osteoporosis research in both pharmaceutical and academic settings.

Prior to joining the MMRF, Dr. Levy was Technical Director at the Binding Site, where she supported the use of Freelite, a diagnostic assay for multiple myeloma. In addition, she worked at Bayer Pharmaceuticals Corporation in West Haven, CT, for nine years. In that capacity, she was engaged in target identification, compound validation, and project leadership in the fields of cancer and osteoporosis research. She has contributed to the delivery of novel drug candidates for clinical studies in each of these indications.

Dr. Levy earned her PhD at the University of Vermont and then completed two postdoctoral fellowships at the Rockefeller University and later at the State University of New York at Stony Brook. Her two academic appointments were at New York University Medical Center and Yale University, studying various aspects of cell signaling pathways involved in the pathogenesis of cancer and development of osteoporosis.

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