Epigenetics, Stem Cells, and Environmental Health Symposium and Workshop

June 1-2, 2017

NIEHS Building 101, Rodbell Auditorium
111 TW Alexander Drive, Research Triangle Park, N.C.
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Day 1 – June 1, 2017

8:00 – 8:30 a.m.  Registration
8:30 – 8:40 a.m.  Welcome and Opening Remarks
                  Darryl Zeldin, M.D., NIEHS
8:40 – 10:40 a.m.  SESSION 1: Pluripotent Stem Cells
                  Session Chair: Jill Dowen, Ph.D., University of North Carolina at Chapel Hill
                  Ge Guo, Ph.D., Wellcome Trust Centre for Stem Cell Research, University of Cambridge
                  Generation and Characterization of Human Naive Pluripotent Stem Cells
                  Guang Hu, Ph.D., NIEHS
                  Post-Transcriptional Regulation of the Pluripotent State
                  Thomas Zwaka, M.D., Ph.D., Icahn School of Medicine at Mount Sinai
                  Ronin’s Role in Creating Regulatory DNA Structures: Blurring the Distinction Between Enhancers and Promoters
                  Konrad Hochedlinger, Ph.D., Harvard Stem Cell Institute
                  DUSP9 Modulates DNA Hypomethylation in Female Mouse Pluripotent Stem Cells
10:40 – 11:00 a.m.  Break
11:00 a.m. – 12:30 p.m.  SESSION 2: Stem Cells and Development
                  Session Chair: Guang Hu, Ph.D., NIEHS
                  Max Wicha, M.D., University of Michigan
                  Breast Cancer Stem Cell States and the Tumor Microenvironment
                  Iannis Aifantis, Ph.D., New York University
                  Long Non-Coding RNA-Mediated Gene Transcription in Hematopoiesis and Leukemia
                  Amander Clark, Ph.D., University of California, Los Angeles
                  Protecting DNA Methylation in Naive and Primed Human Pluripotent Stem Cells
12:30 – 1:30 p.m.  Lunch
1:30 – 3:00 p.m.  SESSION 3: Chromatin Biology
                  Session Chair: Raja Jothi, Ph.D., NIEHS
                  Gerald Crabtree, M.D., Stanford University
                  Chromatin Remodeling: Insights From the Genetics of Human Disease and New Methods
                  Robert Kingston, Ph.D., Massachusetts General Hospital
                  Nucleosome Compaction as a Regulatory Mechanism During Development
                  Ali Shilatifard, Ph.D., Northwestern University
                  Principles of Epigenetics and Chromatin in Development and Human Disease
3:00 – 5:00 p.m.  POSTER SESSION
Day 2 – June 2, 2017

8:00 – 8:30 a.m. Registration

8:30 – 10:00 a.m. SESSION 4: Transcriptional Control  
Session Chair: Paul Wade, Ph.D., NIEHS
Karen Adelman, Ph.D., Harvard University  
Making Sense of Non-Coding Transcription

Ramin Shiekhattar, Ph.D., University of Miami  
Integrator in MAPK Signaling and Cancer

Raja Jothi, Ph.D., NIEHS  
Transcription at Intragenic Enhancers Attenuates Gene Expression

10:00 – 10:20 a.m. Break

10:20 – 11:50 a.m. SESSION 5: Epigenetic Regulation  
Session Chair: Eda Yildirim, Ph.D., Duke University
Kai Ge, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases  
Enhancer Chromatin Modification in Differentiation, Development, and Cancer

Anjana Rao, Ph.D., La Jolla Institute  
Epigenetic and Transcriptional Programs in T Cells During Anti-Viral and Anti-Cancer Responses

Sundeep Kalantry, Ph.D., University of Michigan  
The Orchestration of X-Chromosome Inactivation

11:50 a.m. – 1:00 p.m. Lunch

1:00 – 3:00 p.m. SESSION 6: Stem Cells and Environment  
Session Chair: Erik Tokar, Ph.D., NIEHS
Alvaro Puga, Ph.D., University of Cincinnati  
Ah Receptor-Mediated Disruption of the Cardiac Embryogenesis Program

Dave Sherr, Ph.D., Boston University  
The Role of the AHR in Development of Cancer-Associated and Tissue-Specific Stem Cells

Thea Tlsty, Ph.D., University of California, San Francisco  
Stress Signaling and Novel Entry to Activation of Sox2, Oct3/4, Nanog, and Cellular Plasticity in Rare Human Somatic Cells

Hugh Taylor, M.D., Yale University  
Endometrial Stem Cells Derived From Bone Marrow, Epigenetic Programming, and the Effect of Endocrine Disruption

3:00 – 3:20 p.m. Break

3:20 – 5:00 p.m. WORKSHOP: Future Directions and Outcomes

5:00 – 5:10 p.m. Closing Remarks
Speaker Abstracts
 SESSION ONE: 
Pluripotent Stem Cells

Ge Guo, Ph.D. 
University of Cambridge 
“Generation and Characterization of Human Naive Pluripotent Stem Cells”

Naïve pluripotent stem cells (PSCs) in culture resemble nascent epiblast, which in rodent is transiently formed in pre-implantation blastocyst. Comparative studies of pluripotency indicate that conventional human PSCs may represent post-implantation epiblast cells that are primed for lineage commitment. Our attention has focused on capturing a more naïve transcriptional and epigenetic status similar to the mouse embryonic stem (ES) cell state. We have established candidate human naïve PSC from embryo and from primed PSCs via resetting with the expression of NANOG and KLF2 transgene. Here we developed a simple transgene-free method for resetting human ES cells or induced-PSC to naïve status via transient exposure to histone deacetylase inhibition. This chemical resetting protocol is effective across multiple embryo-derived and induced PSCs. The transcriptome profile of chemically reset cells is similar to that of candidate naïve stem cells derived from the human embryo and diverges markedly from conventional human PSCs. Chemically reset and embryo-derived cells also share a distinctive transposable element expression profile with the human pre-implantation embryo. Importantly, DNA methylation is reduced globally to the level of the inner cell mass. We also exploited the tri-lineage differentiation potential of multiple reset cells lines, particularly compared to their primed pairs. These simple and reliable resetting systems will facilitate wider studies of naïve pluripotency in humans.

Guang Hu, Ph.D. 
NIEHS 
“Post-Transcriptional Regulation of the Pluripotent State”

Poly(A) tail length and mRNA deadenylation play important roles in gene regulation. However, how they regulate embryonic development and pluripotent cell fate is not fully understood. Here we present evidence that CNOT3-dependent mRNA deadenylation governs the pluripotent state. We show that CNOT3, a component of the Ccr4-Not deadenylase complex, is required for mouse epiblast maintenance. It is highly expressed in blastocysts and its deletion leads to peri-implantation lethality. The epiblast cells in Cnot3 deletion embryos are quickly lost during diapause and fail to outgrow in culture. Mechanistically, CNOT3 C terminus is required for its interaction with the complex and its function in embryonic stem (ES) cells. Furthermore, Cnot3 deletion results in increases in the poly(A) tail lengths, half-lives, and steady-state levels of differentiation gene mRNAs. The half-lives of CNOT3 target mRNAs are shorter in ES cells and become longer during normal differentiation. Together, we propose that CNOT3 maintains the
pluripotent state by promoting differentiation gene mRNA deadenylation and degradation, and we identify poly(A) tail-length regulation as a post-transcriptional mechanism that controls pluripotency.

**Thomas Zwaka, M.D., Ph.D.**

Icahn School of Medicine at Mount Sinai

“Ronin’s Role in Creating Regulatory DNA Structures: Blurring the Distinction Between Enhancers and Promoters”

Differences in transcription factor binding to enhancers are generally thought to influence development, and therefore could bear on the most fundamental questions in biology. How do cells differentiate to form new tissues? And how do these tissues function in a coordinated and flexible manner? Here I will present an entirely novel gene regulatory paradigm in which promoters (and their enhancers) interact with other promoters to potentially regulate key gene expression programs. Adding to this novelty is our choice of a candidate genomic organizer, Ronin, which emerged when a fossil transposon was co-opted by ancient metazoans to achieve a level of functional diversity not seen before in evolution.

**Konrad Hochedlinger, Ph.D.**

Harvard University

“DUSP9 Modulates DNA Hypomethylation in Female Mouse Pluripotent Stem Cells.”

Blastocyst-derived embryonic stem (ES) cells and gonad-derived embryonic germ cells (EGCs) represent two classic types of pluripotent cell lines, yet their molecular equivalence remains incompletely understood. Here, we compare genome-wide methylation patterns between isogenic ES cells and EGC lines to define epigenetic similarities and differences. Surprisingly, we find that sex rather than cell type drives methylation patterns in ES cells and EGCs. Cell fusion experiments further reveal that the ratio of X chromosomes to autosomes dictates methylation levels, with female hybrids being hypomethylated and male hybrids being hypermethylated. We show that the X-linked mitogen-activated protein kinase phosphatase DUSP9 is upregulated in female compared to male ES cells, and its heterozygous loss in female ES cells leads to male-like methylation levels. However, male and female blastocysts are similarly hypomethylated, indicating that sex-specific methylation differences arise in culture. Collectively, our data demonstrate the epigenetic similarity of sex-matched ES cells and EGCs and identify DUSP9 as a regulator of female-specific hypomethylation.
SESSION TWO:
Stem Cells & Development

Max Wicha, M.D.
University of Michigan
“Breast Cancer Stem Cell States and the Tumor Microenvironment”

Many cancers, including breast cancer, display a hierarchal organization resembling normal tissue development. At the apex of this hierarchy are cells which display stem cell properties, including the capacity to self-renew as well as to differentiate into cells which lose self-renewal capacity and constitute the tumor bulk. These cancer stem-like cells (CSCs) mediate tumor metastases and contribute to treatment resistance. CSC maintain cellular plasticity, allowing them to transition between mesenchymal- and epithelial-like states. This plasticity plays a critical role in the ability of these cells to successfully form distant metastases. Epithelial-mesenchymal transitions are mediated by signals from the tumor microenvironment or niche which includes stromal and immune cells such as myeloid-derived suppressor cells. In addition, nutrients such as glucose and glutamine as well as oxygen tension mediate EMT-MET transitions via redox reactions involving Hif-1a and NRF. Based on these concepts we have developed strategies to target CSCs based on their metabolic vulnerabilities.

Iannis Aifantis, Ph.D.
New York University
“Long Non-Coding RNA-Mediated Gene Transcription in Hematopoiesis and Leukemia”

Despite the recent identification and cataloguing of thousands of non-coding RNAs, including long non-coding RNAs (lncRNA), we know very little about their biological activities and their putative roles in disease, such as human cancer. Here we describe an optimized CRISPRi screening platform (eCRISPRi). Using this platform, we assign biological activities in lncRNAs that are direct targets of the proto-oncogene MYC using human acute lymphoblastic leukemia (ALL), a frequent and devastating blood tumor as a tumor model. With this approach, we have identified novel lncRNAs that can control the growth of ALL cells, specifically one that resides within a gene desert upstream of the chemokine receptor CXCR4 (lnrCXCR4), itself a gene essential for ALL migration and survival. lnrCXCR4 is conserved only within primates and can control CXCR4 gene expression, chemotaxis to the CXCR4 ligand CXCL12 (SDF1), and leukemia cell survival, both in vitro and in vivo. Additional studies suggested that lnrCXCR4 regulates gene expression by promoting specific, cis-acting chromosomal looping to the CXCR4 promoter and recruitment of transcriptional activator complexes. To our knowledge, this is the first lncRNA that can control migration of cancer cells acting through direct regulation of an adhesion regulator. As a variety of tumors are addicted to CXCR4 function for survival and metastasis, this work could open the way for future protocols targeting lncCXCR4 expression in multiple tumor types.
Amander Clark, Ph.D.
University of California, Los Angeles
“Protecting DNA Methylation in Naïve and Primed Human Pluripotent Stem Cells”

During specific times in human embryo and germline development, the genome undergoes global changes in DNA methylation. This involves the removal of the majority of methylated cytosine bases through active or replication-coupled mechanisms. These globally demethylated states are speculated to make the epigenome vulnerable to environmental-driven epigenetic changes. In previous work, we demonstrated that discreet regions of the stem cell and germline genome are protected from global DNA demethylation. We hypothesized that a diverse range of common, cell-type, and locus- specific mechanisms function to protect DNA methylation at specific regions of the genome. In the current study, we evaluated the role of Tripartite motif containing 28 (TRIM28) protein in protecting discreet sites in the pluripotent stem cell (PSC) genome from DNA demethylation. TRIM28 is ubiquitously expressed in PSCs, germline cells, and somatic cells. We used CRISPR/Cas9 gene editing technologies to create a null mutation in the human TRIM28 gene in primed human PSCs. Data will be presented on the role of TRIM28 in regulating human pluripotent self-renewal, differentiation, DNA methylation protection, chromatin accessibility, and reversion to the naïve state. Our results show that TRIM28 has distinct roles in the primed and naïve states of pluripotency, and that TRIM28 is required to protect specific, yet distinct loci from DNA demethylation in the two unique states of pluripotency.

SESSION THREE:
Chromatin Biology

Gerald Crabtree, M.D.
Stanford University
“Chromatin Remodeling: Insights from the Genetics of Human Disease and New Methods”

Driving mutations within the subunits of Brg1 associated factor (BAF; mSWI/SNF) complexes are found in over 20% of all human malignancies and a large number of human neurologic diseases. To explore the mechanism of action of these complexes we examined genomic accessibility and histone marks after either rapid conditional deletion of the genes encoding subunits of these complexes or after introducing oncogenic mutations in subunits of the complex. We find that loss of BAF subunits leads to large-scale reduction in genomic accessibility and accumulation of polycomb repressive complexes (PRC) over the genome. To understand the underlying mechanism, we developed the chromatin indicator and assay (CIA) mouse allowing the rapid and reversible increase in the concentration of a chromatin regulatory complex at any genetic locus. Recruiting BAF to a polycomb-repressed locus results in the eviction of polycomb within minutes by an ATP-dependent mechanism. Loss of PRC1 and PRC2 is followed by decay of their histone modifications and the development of accessible DNA within 30 minutes. We find a
direct interaction between BAF and PRC1, which is essential for the ATP-dependent eviction of polycomb. Surprisingly, we find no evidence of nucleosome eviction, sliding, or turnover upon recruitment of BAF complexes to the repressed Oct4 locus, despite the development of accessibility. These studies indicate that the mechanism underlying the critical opposition between BAF and polycomb is a direct, ATP-dependent interaction between BAF and PRC1. This results in PRC1 and PRC2 removal and the development of accessible DNA without transcription, polymerase II occupancy, or cellular replication.

I will also describe an unexpected way that BAF complexes contribute to the dissolution and formation of heterochromatin by an interaction with topo II involving the production of strand-cleaved intermediates. These studies indicate that DNA catenation may be fundamental to the formation of heterochromatin

Robert Kingston, Ph.D.
Massachusetts General Hospital
“Nucleosome Compaction as a Regulatory Mechanism During Development”

Nucleosomes can play a role in modulating gene expression via two distinct types of mechanisms. They can become covalently modified to direct domains that are either permissive or repressive for transcription. Alternatively, they can assume positions and/or inherent characteristics that are permissive or repressive for transcription factor function and binding. We have explored compaction of nucleosomes in vitro and in vivo, which stabilizes them to remodeling and might lead to formation of repressed domains. We find that the polycomb repressive complex PRC1 is involved in two types of compaction. It can create a compacted structure containing four nucleosomes. Point mutations in the residues needed to form this structure relieve repression of gene expression in embryonic stem (ES) cells and generate anterior-posterior transformations in mice that phenocopy Polycomb group (PcG) null mutations. These data imply that this compaction mechanism is central to PcG function during mouse development. PRC1 components are also involved in compacting large domains, perhaps via a distinct mechanism from those required to compact several nucleosomes. We are studying compaction of large domains in ES cells and in neural progenitors using 5C and STORM imaging. We have identified domains that are smaller than TAD domains and that appear to isolate repressed regions from being involved in long-range interactions that promote activation. We propose that the regulation of nucleosome compaction is a key aspect of PcG function.

Ali Shilatifard, Ph.D.
Northwestern University
“Principles of Epigenetics and Chromatin in Development and Human Disease”

Epigenetic regulation of gene expression in metazoans is central for establishing cellular diversity. Perturbation of this process results in pathological conditions. Although transcription
factors are essential for implementing gene expression programs, they do not function in isolation and require the recruitment of various chromatin-modifying and remodeling machineries. A classic example of developmental gene expression through chromatin is the regulation of the balanced activities of the Polycomb group (PcG) proteins within the polycomb repressive complexes (PRC1 and PRC2), and the Trithorax group (TrxG) proteins within the COMPASS family. Recent large-scale genome sequencing efforts of human cancer have demonstrated that PcG and COMPASS subunits are highly mutated in a large number of human solid tumors and hematological malignancies. I will discuss our laboratory’s latest biochemical and genetic studies defining the molecular properties of COMPASS and PcG families in the regulation of gene expression during development, and the central role they play in cancer pathogenesis. I will further share how we have taken advantage of such basic molecular information to develop targeted therapeutics for the treatment of hematological malignancies, pediatric brain cancer, and other forms of solid tumors.

SESSION FOUR: Transcriptional Control

Karen Adelman, Ph.D.
Harvard University
“Making Sense of Non-Coding Transcription”

Cell differentiation and development involve coordinated changes in gene expression and chromatin architecture. Paramount to this process is the evolution of specific enhancer landscapes that direct cell-type specific patterns of transcription activation and repression. Importantly, enhancers are characterized by the binding of lineage-specifying transcription factors to regions of accessible chromatin, and are marked with certain histone modifications. Moreover, enhancers recruit the transcription machinery and are actively transcribed by RNA polymerase II (Pol II), with levels of enhancer RNA synthesis reflecting enhancer strength. However, enhancer RNAs are poorly conserved in both sequence and position, raising questions about their functionality as RNA species. Indeed, we suggest that it is often the act of transcription rather than the nature of the RNA transcribed that provides regulatory information.

We find that recruitment of Pol II to enhancers, as well as the pausing of Pol II during early transcription elongation is paramount to the appearance and potency of enhancers during development. We provide evidence that paused Pol II is key for maintenance of open chromatin within enhancer loci and for stabilization of transcription factor occupancy. Thus, in addition to synthesizing enhancer RNA species, the occupancy of enhancers by Pol II sculpts local chromatin architecture, enabling cell-type specific profiles of gene expression.
Activating mutations in the mitogen-activated protein kinase (MAPK) cascade, also known as the RAS-MEK-ERK1/2 pathway, are the underlying cause of over 70% of human cancers. Pharmacological intervention with kinase inhibitors has been hampered due to the rapid emergence of drug resistance. Moreover, while there have been great strides made on elucidating the cytoplasmic components of MAPK signaling, the key downstream targets coordinating the transcriptional response have not been elucidated. To uncover additional actionable targets, there is a great need for detailing the nuclear effectors of the MAPK pathway. Here, we demonstrate that MAPK transcriptional response in human cells is funneled through integrator, an RNA polymerase II-associated complex. We show that integrator and activated ERK1/2 are components of a positive feedback loop on chromatin. Genome-wide analyses demonstrate that integrator is essential for recruitment of phospho-ERK1/2 to immediate early genes. ERK1/2 phosphorylates INTS11, the catalytic subunit of integrator, leading to additional cycles of integrator recruitment and transcriptional induction. Integrator plays a unique role in the MAPK pathway since depletion of a number of key subunits of the co-activator complex, mediator, does not alter MAPK gene expression responsiveness. Finally, depletion of INTS11 diminished MAPK transcriptional programs in human cancers with activating mutations in BRAF or KRAS, pinpointing to INTS11 as an important therapeutic target in many human cancers.

Eukaryotic gene transcription is regulated at multiple rate-limiting steps, including RNA Polymerase II (Pol II) recruitment, transcription initiation, promoter-proximal Pol II pause release, and transcription termination. However, the mechanisms regulating transcription during productive elongation remain poorly understood. Enhancers, which activate gene transcription, themselves undergo Pol II-mediated transcription, but our understanding of enhancer transcription and RNAs (eRNAs) remains incomplete. Although about half of all annotated enhancers are intragenic, most studies of enhancer function were conducted by cloning the enhancer of interest, even if it is intragenic, either upstream or downstream of transient/transgenic reporters. Consequently, we have yet to fully appreciate the effects of intragenic enhancer-transcription on host gene expression. I will discuss our recent work showing transcription at intragenic enhancers interfering with and attenuating host gene transcription during productive elongation. While the extent of attenuation correlates positively with nascent eRNA expression, the act of intragenic enhancer-transcription alone, but not eRNAs, explains the attenuation. Through CRISPR/Cas9-mediated deletions, we demonstrate a physiological role for intragenic enhancer-mediated transcription attenuation in cell-fate determination. Our findings suggest that intragenic enhancers serve more regulatory functions than previously appreciated. Further, the act of transcription at intragenic...
Enhancers alone could represent a general mechanism to attenuate and fine-tune host gene transcription during productive elongation. We propose that intragenic enhancers not only enhance transcription of one or more genes from a distance but also fine-tune transcription of their host gene through transcription interference, facilitating differential utilization of the same regulatory element for disparate functions.

SESSION FIVE:
Epigenetic Regulation

Kai Ge, PhD
National Institute of Diabetes and Digestive and Kidney Diseases
“Enhancer chromatin modification in differentiation, development, and cancer”

Enhancers play a central role in cell-type-specific gene expression. There are two major types of enhancers in mammalian cells: primed and active. Primed enhancers are marked by histone H3K4 mono-methylation (H3K4me1) while active enhancers are further marked by H3K27 acetylation (H3K27ac). We previously identified CBP and p300 as major H3K27 acetyltransferases (EMBO J 2011). We also identified MLL3 (KMT2C) and MLL4 (KMT2D) as major H3K4 mono-methyltransferases enriched on enhancers. During differentiation of adipocytes, myocytes, B & T cells and development of heart and mammary gland, MLL3/4 are required for enhancer activation, cell-type-specific gene expression, cell differentiation and tissue development.

In embryonic stem (ES) and somatic cells, MLL3/4 associate with, but are surprisingly dispensable for the maintenance of, active enhancers of cell identity genes. As a result, MLL3/4 are dispensable for maintaining cell identity gene expression. In contrast, MLL3/4 are required for enhancer-binding of H3K27 acetyltransferases CBP/p300, enhancer activation, and induction of cell identity genes during differentiation. MLL3/4 proteins, rather than MLL3/4-mediated H3K4me1, control CBP/p300 recruitment to enhancers. MLL3/4 are also required for somatic cell reprogramming into iPS cells. Thus, while enhancer-priming by MLL/4 is dispensable for cell identity maintenance, it controls cell fate transition by orchestrating CBP/p300-mediated enhancer activation.

Our data suggest a 3-step model on how chromatin modifying enzymes regulate enhancer activation: 1) pioneer transcription factors (TFs) bind to enhancer-like elements; 2) pioneer and lineage-determining TFs cooperatively recruit MLL3/4 to prime enhancer regions with H3K4me1; 3) MLL3/4 facilitate the binding of CBP/p300, which activate enhancers with H3K27ac. The H3K27ac mark is recognized by Brd4, which recruits Mediator and RNA polymerase II to establish enhancer-promoter interactions and activate cell-type-specific gene expression.
We reported that MLL3/4 associate with H3K27 demethylase UTX in one protein complex (JBC 2007; PNAS 2007). UTX protein, but not its H3K27 demethylase activity, is required for cell differentiation and mouse development (PNAS 2012; JCI & MCB 2016), suggesting that UTX likely functions through MLL3/4 to regulate enhancer activation during differentiation and development. Interestingly, while UTX demethylase activity is dispensable for normal muscle development, it is required for muscle stem cell-mediated myofiber regeneration (JCI 2016).

MLL3/4 and UTX are tumor suppressors frequently mutated in many types of cancers. Our findings suggest that mutations in MLL3/4 and UTX would lead to defects in enhancer activation, cell-type-specific gene expression and cell differentiation. Such a mechanism may contribute to the pathogenesis of these cancers.

Anjana Rao, Ph.D.
La Jolla Institute
“Epigenetic and Transcriptional Programs in T Cells During Anti-Viral and Anti-Cancer Responses”

During persistent antigen stimulation, CD8+ T cells show a gradual decrease in effector function, referred to as exhaustion, which impairs responses in the setting of tumors and infections. We have comprehensively analyzed changes in chromatin accessibility and gene expression in CD8+ T cells during acute and chronic viral infections in vivo and upon stimulation in vitro. We have further defined a pattern of chromatin accessibility specific for T cell exhaustion, characterized by enrichment for consensus binding motifs for NFAT and Nr4a transcription factors. Anti–PD-L1 treatment of tumor-bearing mice resulted in cessation of tumor growth and increased granzyme and serpin expression by the tumor-infiltrating cells, with only limited changes in gene expression and chromatin accessibility. Our studies provide a valuable resource for the molecular understanding of T-cell exhaustion in cancer and other inflammatory settings.

Sundeep Kalantry, Ph.D.
University of Michigan
“The Orchestration of X-Chromosome Inactivation”

The disparity in X-chromosomal dosage between male and female mammals is remedied via transcriptional inactivation of most genes along one of the two X-chromosomes in females. This process is referred to as X-chromosome inactivation. X-inactivation is a paradigm of epigenetic regulation, since one of two equal X-chromosomes is inactivated early in embryogenesis and replicated copies of that X-chromosome are transmitted as inactive through all future rounds of cell division. Conventionally, X-inactivation is thought to initiate via the upregulation of the Xist long noncoding RNA from the future inactive X-chromosome. Upon its expression, the Xist RNA recruits protein complexes to the inactive-X that then epigenetically silence X-linked genes and thereby trigger X-inactivation. We compared the ability of Xist RNA to silence X-linked genes in males and females through in vitro and in vivo experiments and found that Xist RNA is
insufficient to trigger X-inactivation in males. The data further predict that a novel X-chromosomal factor that escapes X-inactivation, and therefore is expressed from both the inactive and the active X-chromosomes, is required to initiate X-inactivation. The higher dose of this factor in XX females relative to XY males explains why females undergo X-inactivation and males do not. We describe the discovery and functional characterization of such a factor.

SESSION SIX
Stem Cells and Environment

Alvaro Puga, Ph.D.
University of Cincinnati
“Aryl Hydrocarbon Receptor-Mediated Disruption of the Cardiac Embryogenesis Program”

The Aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that mediates gene regulatory responses to many polycyclic and halogenated environmental agents. AHR activation by dioxin (2,3,7,8-tetrachlorodibenzo-p-dioxin; TCDD), its prototypical ligand, during differentiation of mouse embryonic stem (ES) cells into cardiomyocytes disrupts the expression of multiple homeobox transcription factors and inhibits cardiomyocyte contractility. Treatment of mouse ES cells with TCDD at daily differentiation intervals revealed that TCDD-induced loss of contractility had a developmental window of sensitivity. Contractility was an AHR-dependent TCDD target solely between differentiation days 0 and 3, during the period of pan-mesoderm development. At this time, TCDD also disrupted expression of genes in the TGFβ/BMP2/4 and WNT signaling pathways; suppressed the secretion of BMP4, WNT3a, and WNT5a; and elevated the secretion of Activin A. Supplementing the culture medium with BMP4, WNT3a or WNT5a during the first three days of differentiation successfully countered TCDD-induced impairment of contractility, while anti-WNT3a, or anti-WNT5a antibodies or continuous Noggin (a BMP4 antagonist) or activin A treatment inhibited the contractile phenotype. In Ahr+/+, but not in Ahr−/− ES cells, TCDD treatment significantly increased mitochondrial copy number, suggestive of mitochondrial stress and remodeling. Sustained AHR activation during ES cell differentiation appears to disrupt the expression of signals critical to the ontogeny of cardiac mesoderm and cause the loss of contractility in the resulting cardiomyocyte lineage.

Dave Sherr, Ph.D.
Boston University
“The Role of the Aryl Hydrocarbon Receptor in Development of Cancer-Associated and Tissue-Specific Stem Cells”

Self-renewing, chemoresistant cancer stem cells (CSCs) are believed to contribute significantly to cancer invasion, migration, and patient relapse. Therefore, the identification of signaling pathways that regulate the acquisition of stem-like qualities is an important step towards
understanding why patients relapse and towards development of novel therapeutics that specifically target CSC vulnerabilities. Recent studies identified a role for the aryl hydrocarbon receptor (AHR), an environmental carcinogen receptor implicated in cancer initiation, in normal tissue-specific stem cell self-renewal. These studies inspired the hypothesis that the AHR plays a role in the acquisition of CSC-like qualities. To test this hypothesis, AHR activity in human breast and oral cancer cells were modulated with sets of diverse AHR ligands, shRNA, AHR-specific gene editing, or AHR-specific inhibitors, and phenotypic, genomic, and functional stem cell-associated characteristics were evaluated. The data demonstrate that: 1) human breast or oral cancer cells expressing high levels of aldehyde dehydrogenase (ALDH) activity, a marker for stem-like cells, exhibit elevated levels of Ahr, and \textit{Cyp1b1} and \textit{Cyp1a1}, AHR-driven genes. 2) AHR hyper-activation with several ligands, including environmental and bacterial-derived ligands, significantly increases ALDH1 activity, expression of stem cell- and invasion/migration-associated genes, and accelerates cell migration. 3) The AHR interacts directly with Sox2 and \textit{Runx1}, master regulators of self-renewal in breast cancer cells. 4) AHR inhibition or knockdown significantly reduces stem cell-dependent tumorsphere formation in low adherence conditions, stem cell-associated ALDH activity, the rapid migration of ALDH\textsuperscript{high} stem-like cells, ALDH\textsuperscript{high} cell chemoresistance, likely through reduction in the ABCG2 transporter, and inhibits tumor initiation. Furthermore, high baseline (constitutive) levels of AHR activity are mediated at least in part by a positive feedback loop in which the AHR drives expression of the indole oxygenase TDO, which generates tryptophan-derived AHR ligands. Data obtained in a system of induced pluripotent stem cell-derived non-malignant cells suggests that a similar relationship exists between constitutive AHR activity, TDO expression, and normal tissue-specific blood stem cells involved in the physiological development of megakaryocyte and erythroid lineages.

These data suggest that the AHR plays an important role in development of normal tissue-specific and cancer-associated stem cells and that environmental AHR ligands may alter the development of both normal and cancer-associated stem cells.

\textbf{Thea Tlsty, Ph.D.}

University of California, San Francisco

“Stress Signaling and Novel Entry to Activation of Sox2, Oct3/4, Nanog, and Cellular Plasticity in Rare Human Somatic Cells”

Tissues exposed to injury, inflammation, or irritation induce a program of stress signals implemented by a cocktail of cytokines and molecular messengers. These signals have the potential to activate extensive lineage plasticity in a rare subpopulation of human cells. We previously identified and characterized a rare population of somatic cells isolated from adult human disease-free tissues that have the ability to activate the pluripotency factors Sox2, Oct3/4, and Nanog. When in an activated state these cells can generate multiple tissue derivatives of ectodermal, mesodermal, and endodermal lineages in both in vitro and in vivo assays. These endogenous plastic somatic (ePS) cells are mortal and genomically stable. Therefore, these cells have potential as a non-embryonic resource for regenerative medicine. We have characterized the cellular and molecular mechanisms by which these mortal ePS cells
acquire plasticity. This plasticity depends on activating SON through a pathway that is not expressed or used by human embryonic stem cells or induced pluripotent stem cells, identifying this signaling as a novel portal to plasticity in human cells. We have been able to develop multiplex analysis that allows visualization of cells expressing ePS markers in human tissue. The role of DNA damaging agents in activating this program will be discussed.

Hugh Taylor, M.D.
Yale University
“Endometrial Stem Cells Derived from Bone Marrow, Epigenetic Programming and the Effect of Endocrine Disruption”
Biographies
Karen Adelman, Ph.D.
Harvard University

Karen Adelman, Ph.D., is a professor of biological chemistry and molecular pharmacology at Harvard Medical School. Prior to moving to Harvard Medical School, she was a senior investigator at the National Institute of Environmental Health Sciences (NIEHS), in the Epigenetics and Stem Cell Biology Laboratory. Her work revealed that a majority of metazoan gene regulation occurs during early transcription elongation, through controlled pausing of RNA polymerase II. Her recent findings that pause release is a key determinant of gene activity in response to developmental and environmental factors has provided new insights into signal-responsive gene expression, and its perturbation in cancer cells. Ongoing work probes the impact of pausing of RNA polymerase II at enhancer loci, the subsequent regulation of enhancer RNA (eRNA) synthesis, and how eRNA production influences protein-coding gene expression.

Iannis Aifantis, Ph.D.
New York University

Widely known for his expertise in the fields of hematopoiesis, and acute leukemia, Iannis Aifantis, Ph.D., is a professor, and the chair of the Department of Pathology at New York University (NYU) School of Medicine. Aifantis attended the University of Crete in Greece, earned his doctorate from the University of Paris V, Rene Descartes, and completed his postdoctoral training at Harvard University, Dana Farber Cancer Institute. He started his independent career at University of Chicago in 2003 and joined NYU in 2006. Throughout his career, he has earned many prestigious honors including the 2010 Vilcek Award for Creative Promise, and the 2011 McCulloch & Till Award from the International Society for Hematology and Stem Cell Biology. Moreover, in 2009, he was selected as an Early Career Scientist by the Howard Hughes Medical Institute (HHMI). He is one of the leaders of the fields of hematopoiesis and leukemia, with diverse focus areas that include the study of protein stability, epigenetic regulation, and tumor microenvironment. His lab was instrumental in the understanding of the molecular mechanisms of initiation, and progression of both acute lymphoid, and myeloid leukemia.

Amander Clark, Ph.D.
University of California, Los Angeles

Amander Clark, Ph.D., is professor, and vice chair of the Department of Molecular, Cell, and Developmental Biology at the University of California (UCLA), Los Angeles. She is a key member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and co-director of the Embryonic Stem Cell Derivation Laboratory. She is also a member of the Jonsson Comprehensive Cancer Center, and the Molecular Biology Institute. Clark’s group was the first to map DNA methylation reprogramming in the human germline during prenatal life at single base resolution using next generation sequencing. This work exposed one of the most
vulnerable time windows in human germline development, opening new areas of investigation into germline environmental exposures during prenatal life. Her lab was also the first to use next generation sequencing to discriminate sex-specific transcriptional differences between male, and female human prenatal germline cells, leading to the definition of the advanced stages of human primordial germ cell development. Clark’s research is primarily funded by the National Institute of Child Health and Human Development, with previous awards from the California Institute for Regenerative Medicine, Fuller Foundation, and the Iris Cantor UCLA Women's Health Center. Clark is a recipient of Young Investigator Award from the Lance Armstrong, a Research and Career Development award from STOP Cancer, a Research award from the Concern Foundation, and a Young Investigator Award from the International Society for Stem Cell Research. Clark is a member of the Hinxton Group, an international consortium of scientists, ethicists, and policy makers for the use of pluripotent stem cell derived gametes.

Gerald Crabtree, M.D.
Stanford University

Crabtree began his career as an independent researcher with the discovery that one gene could produce different functional proteins by alternative splicing of messenger RNA (mRNA) transcripts. Later he used, and developed early bioinformatics techniques to show that the human genome contained remnants of ancient transposition events. In the late 1980’s, and early 1990’s, Crabtree worked with Stuart Schreiber to define the Ca²⁺/calcineurin/ NFAT signaling pathway, which carries signals from cell surface calcium channels to the nucleus to activate genes. These discoveries resulted in the first understanding of the mechanism of action of the commonly used immunosuppressant drugs: cyclosporin and FK506. Later his laboratory, and others, used genetic approaches in mice to show that calcineurin-NFAT signaling plays essential roles in the development of the heart, immune, skeletal, and nervous systems, and its dysregulation is likely to be responsible for many of the phenotypes of Down Syndrome. This signaling pathway was one of the first to bridge events at the cell membrane to the nucleus. In 1993 Crabtree and Schreiber designed and synthesized the first synthetic ligands to induce proximity of proteins within cells. He and Schreiber generalized this approach to other types of synthetic ligands including natural molecules involved in plant signaling that have expanded the usefulness of this approach. In the early 1990’s, Crabtree defined the mammalian SWI/SNF complex (also called BAF complex) by purifying, and cloning the genes that encode its subunits or components. Using biochemical, and genetic approaches he discovered that its subunits are put together like letters in a word to give a wide variety of different biological, and pathogenic meanings. In 2009, he discovered an epigenetic, and genetic circuitry controlling development of the mammalian nervous system, and demonstrated that recapitulating this circuitry in mammalian cells can convert human skin cells to neurons. Recently by purifying the complete set of subunits of BAF (mSWI/SNF) chromatin remodeling complexes, his laboratory has shown that mutations in these subunits are a frequent cause of several human neurologic diseases, and contribute to the cause of over 20% of human cancers, potentially opening a new avenue for treatment of certain cancers.
Jill Dowen, Ph.D.
The University of North Carolina at Chapel Hill

Jill Dowen is an Assistant Professor at The University of North Carolina at Chapel Hill, where she is a member of the Biochemistry and Biophysics Department and the Biology Department. She is also a member of the Lineberger Comprehensive Cancer Center and the Integrative Program in Biological and Genome Sciences. Her lab investigates the link between genome organization and gene expression. Jill is currently a “Kimmel Scholar”. This is an early career award for cancer researchers given out by the Sidney Kimmel Foundation for Cancer Research.

Kai Ge, Ph.D.
National Institute of Diabetes and Digestive and Kidney Diseases

Kai Ge, Ph.D. is a Senior Investigator and Section Chief at the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIDDK/NIH) located in Bethesda, Maryland. He is an internationally recognized expert on histone methyltransferases and demethylases and their roles in the regulation of adipogenesis (generate of fat tissue). Dr. Ge received his BS degree from Fudan University in Shanghai in 1992 and doctorate from Shanghai Institute of Biochemistry, Chinese Academy of Sciences in 1997. After postdoctoral training with Robert Roeder at The Rockefeller University, he was recruited to NIH and promoted to Senior Investigator with tenure in 2011.

Ge Guo, Ph.D.
University of Cambridge

Ge received her first degree in biology from Nankai University in China. In 1998, she joined the doctoral program at Baylor College of Medicine and did her doctoral studies on establishment of tools for recessive genetic screens in mouse embryonic stem cells under the supervision of Allan Bradley. Later she relocated to United Kingdom, and in 2005 she obtained a doctoral degree from University of Cambridge. In 2006, she joined Austin Smith's laboratory with a Medical Research Council Career Development Fellowship to investigate factors regulating mouse pluripotency. She is currently a senior research associate in Austin Smith’s group in University of Cambridge and her main research interest is to study naïve pluripotency in humans.

Konrad Hochedlinger, Ph.D.
Harvard University

Konrad Hochedlinger, Ph.D., is a professor of stem cell and regenerative biology at Harvard University, and a member of the Department of Molecular Biology, and Center for Regenerative Medicine at the Massachusetts General Hospital. He completed his undergraduate training at
the University of Vienna, and his graduate, and post-graduate training with Rudolf Jaenisch at
the Massachusetts Institute of Technology. Hochedlinger’s lab studies the molecular
mechanisms that control normal development, tissue regeneration, and cancer. His lab has
made important contributions to our understanding of how transcription factors rewire the
epigeneric state of cells during cellular reprogramming and related fate transitions.
Hochedlinger is the recipient of the International Society for Stem Cell Research Outstanding
Young Investigator Award, the Harland Winfield Mossman Award for Developmental Biology,
and a Howard Hughes Medical Institute Early Career Award.

**Guang Hu, Ph.D.**
National Institute of Environmental Health Sciences

Guang Hu, Ph.D., heads the Stem Cell Biology Group within the Epigenetics and Stem Cell
Biology Laboratory at the National Institute of Environmental Health Sciences (NIEHS), and
holds a secondary appointment in the NIEHS Reproductive and Developmental Biology
Laboratory. Hu earned his doctorate in 2003 at Baylor College of Medicine, and was a Helen
Hay Whitney Foundation fellow from 2004 to 2007. He completed a postdoctoral fellowship at
Harvard Medical School under Stephen Elledge, Ph.D., before joining NIEHS in 2009.

**Raja Jothi, Ph.D.**
National Institute of Environmental Health Sciences

Jothi earned his bachelor’s degree in 1998 from the University of Madras in India, and his
doctorate in 2004 from the University of Texas at Dallas. He completed his postdoctoral training
in systems biology and epigenetics at the National Center for Biotechnology Information, and
the National Heart, Lung, and Blood Institute respectively, before joining the National Institute
of Environmental Health Sciences (NIEHS) in 2009 as an investigator. He received tenure and
was promoted to senior investigator in 2015. Jothi received the NIEHS Early Career "Rising
Star" Award in 2009, and the Ruth L. Kirschstein Mentoring Award in 2016. The Jothi Lab aims
to understand how transcription regulators, and epigenetic modifications, regulate gene
expression programs during cellular development and differentiation, and apply this knowledge
to aid in the development of diagnostic and therapeutic strategies for cancer and other
diseases.

**Sundeep Kalantry, Ph.D.**
University of Michigan

Sundeep Kalantry is an associate professor in the Department of Human Genetics at the
University of Michigan Medical School. He received his doctorate from the Weill Cornell
Graduate School of Medical Sciences at Cornell University in 2001, where he trained under
Elizabeth Lacy at the Sloan-Kettering Institute in embryology and genetics. In 2002, he moved
to The University of North Carolina at Chapel Hill for a post-doctoral fellowship with Terry Magnuson on epigenetic regulation, including X-chromosome inactivation, by the Polycomb group proteins and long non-coding RNAs. In 2009, Kalantry was recruited to the University of Michigan as a Biological Sciences Scholar. Kalantry’s laboratory studies X-inactivation as well as other epigenetic processes that characterize the early embryo using mouse models. Kalantry’s honors include a National Institute of Health (NIH) Pathway to Independence Award (K99/R00), an NIH Director’s New Innovator Award (DP2), an Ellison Medical Foundation New Scholar in Aging Award, and a March of Dimes Basil O’Connor Starter Scholar Research Award.

Robert Kingston, Ph.D.
Massachusetts General Hospital

Robert Kingston is the Chief of the Department of Molecular Biology at the Massachusetts General Hospital (MGH), is a professor and vice chair of the Department of Genetics at Harvard Medical School, and is an associate member of the Broad Institute. He is also past chair of the Executive Committee on Research at MGH.

Kingston began working on bacterial transcription mechanism in 1977 as a student with Michael Chamberlin in 1977. He received his doctorate from the University of California at Berkeley in 1981 for work on understanding the regulation of Ribosomal RNA (rRNA) synthesis. He trained as a Jane Coffin Childs Fellow with Philip Sharp at the Massachusetts Institute of Technology, where he switched to studying transcriptional regulatory mechanisms in humans. Kingston joined the Department of Molecular Biology at MGH and the Department of Genetics at Harvard Medical School in 1985 as an assistant professor of genetics. He became a professor of genetics in 1995. His work over the past twenty years has been primarily on understanding the regulation of chromatin structure and how that impacts gene regulation in mammals, with a focus on the epigenetic mechanisms that maintain gene expression states during development.

Kingston is the former head of the Biological and Biomedical Sciences (BBS) graduate program at Harvard Medical School. He has organized numerous international conferences on transcription, and on epigenetics, and chromatin structure, and function. He serves on several editorial boards, is a founding Editor of Current Protocols in Molecular Biology, and has served as an Editor at the journal Molecular and Cellular Biology. Kingston is a member of the National Academy of Sciences and a member of American Academy of Arts and Sciences.

Alvaro Puga, Ph.D.
University of Cincinnati

Alvaro Puga is professor of molecular biology and environmental health, in the Department of Environmental Health, at the University of Cincinnati College of Medicine. He is also the Associate Director of the Center for Environmental Genetics at the University of Cincinnati.
College of Medicine. Puga earned a Licenciate in Biology in 1966 from the Universidad Complutense of Madrid, Spain and a doctorate in Molecular Biology and Biophysics in 1972 from Purdue University, Indiana. He completed postdoctoral training in 1976 at the Scripps Clinic and Research Foundation in La Jolla, California. Before joining the University of Cincinnati, he was head of the unit on pharmacogenetics, Laboratory of Developmental Pharmacology, at the National Institute of Child Health and Human Development, and later Deputy Chief of the Laboratory. His research deals with the role of the aryl hydrocarbon receptor on epigenetic responses to environmental exposures as they relate to gene-environment interactions responsible for developmental disease. The focus of this research is centered on: the analysis of signal transduction and epigenetic mechanisms activated in response to toxic environmental agents; studying the molecular mechanisms associated with the development of congenic cardiac disease; and with the disruption of chromatin remodeling that takes place during differentiation, at a time when gene induction may be derailed by exposure to environmental agents, like heavy metals and dioxin-like compounds.

Anjana Rao, Ph.D.
La Jolla Institute for Allergy and Immunology

Anjana Rao obtained her doctorate in biophysics from Harvard University and was a professor at Harvard Medical School until 2010 when she moved to the La Jolla Institute and University of California, San Diego. Her research is focused on regulation of gene expression, using immune cells as a model system. Her lab purified and molecularly characterized the transcription factor NFAT; defined diverse transcriptional programs regulated by NFAT proteins in T cells; identified the pore subunit of the store-operated Ca\(^{2+}\) channel, ORAI1; and discovered that proteins of the TET family are enzymes that alter DNA methylation status by oxidizing 5-methylcytosine. In recent studies, she has defined the role of NFAT in diminished responsiveness in tumor-infiltrating T cells, and the roles of TET proteins and oxidized methylcytosines in the immune, haematopoietic and nervous systems, and in embryonic development and oncogenesis. Rao is an elected member of the United States National Academy of Sciences, the American Academy of Arts and Sciences, and the American Association for the Advancement of Science.

Dave Sherr, Ph.D.
Boston University

Sherr obtained his bachelor’s degree from Brandeis University in 1973 (Summa Cum Laude), and doctorate in Immunology/microbiology from Cornell University in 1978. His doctoral thesis focused on interactions between fetal and neonatal T and B cells during the maturation of high affinity B cell subsets. His postdoctoral work was conducted from January 1978 until April 1980 at Harvard Medical School in the laboratory of Baruj Benacerraf (1980 Nobel Laureate in Medicine). That work involved seminal studies on regulatory subsets of the developing immune system, including suppressor T cells (now referred to as regulatory T cells), in maintaining B and T cell tolerance. He was appointed to the faculty as an instructor in pathology at Harvard
Medical School in 1981, assistant professor in 1982, and associate professor in 1987. In 1990, Sherr began adapting his studies on B and T cell development to investigate the effects of environmental chemicals, especially environmental aryl hydrocarbon receptor (AHR) ligands, on immune system development and in cancer. Three years later, he was recruited to Boston University (BU) as professor of environmental health in the BU School of Public Health with a secondary appointment in the Pathology and Laboratory Medicine Department in the BU School of Medicine. Since moving to BU in 1993, his laboratory has focused primarily on the AHR and its role in oral and breast cancer metastasis and on the effect of environmental AHR ligands on lymphocyte development.

Sherr received his first independent grant in 1981, his first NIH RO1 in 1987, and has been funded continually by the RO1, P01, and P42 mechanisms since then. He has published 120 peer-reviewed manuscripts, many in top flight journals including Nature, Nature Genetics, Nature Immunology, Oncogene, and the Journal of Experimental Medicine. Sherr has served as the founding Director of the Boston University Flow Cytometry Core. He has also served as the Director of the Boston University Immunology Training Program and currently serves as the Director of the Boston University Superfund Research program and Director of the Art BeCAUSE Breast Cancer Foundation Consortium. He has trained 12 doctoral students, 4 masters students, and 24 postdoctoral fellows and has served on 62 doctoral thesis committees.

**Ramin Shiekhattar, Ph.D.**
University of Miami

Ramin Shiekhattar is the Director of Cancer Epigenetics Program, Chief of Division of Cancer Genomics and Epigenetics, and Professor of Human Genetics at the University of Miami Miller School of Medicine. His laboratory has made a number of important contributions over the past years in identifying and characterizing important mediators of epigenetic regulation and noncoding RNA processing that contribute to cancer development. Importantly, the laboratory’s recent work has begun to explore a class of long noncoding RNAs that arise from enhancer elements and behave similar to transcriptional enhancers. The laboratory has identified the RNA polymerase II-associated multiprotein complex, Integrator, as a critical component of the biogenesis machinery for these enhancer RNAs (eRNAs). The laboratory is interested in deciphering the function of Integrator and eRNAs in the context of relevant models of development and disease, using state of the arts genomics and proteomics approaches. These data will be coupled with the development of novel computational methods to decipher the changes in the epigenetics landscape at enhancers, and promoters that helps to define the role of Integrator, and eRNAs in development and cancer.
Ali Shilatifard, Ph.D.
Northwestern University

Ali Shilatifard, professor and chairman of the Department of Biochemistry and Molecular Genetics of the Northwestern University Feinberg School of Medicine, is a world renown biochemist, and molecular biologist, and a respected expert in the field of transcription, and epigenetics, specifically as it relates to cancer biology. Shilatifard has an immense interest in understanding the intricate molecular mechanisms of the regulation of gene expression, the mechanisms that activate or suppress a particular gene’s trait. As a Jane Coffin Childs postdoctoral fellow, Shilatifard made a seminal contribution to the field of leukemia biology by identifying the first function of any of the mixed lineage leukemia (MLL) translocation partners, which is when a section of one chromosome changes place with that of another chromosome creating a mutation. Since then, he has continued to contribute to the field of transcription, chromatin biology, and cancer biology through many discoveries including those of the COMPASS and SEC complexes, which are demonstrating to be central to the mechanisms involved in the development of leukemia and other in cancer development. The Shilatifard lab’s focused studies over the past 15 years have made significant inroads to understanding the cause of childhood leukemia, and his studies are leading to the development of extremely promising target-specific drugs for childhood leukemia, and other forms of cancers. Currently, the inhibitors developed in Shilatifard’s laboratory towards the COMPASS family are being tested for the treatment of childhood leukemia, brain cancer, and triple negative breast tumors.

For his contributions to our understanding of cancer biology, Shilatifard has been recognized by the Leukemia and Lymphoma Society, as the recipient of the Sword of the American Cancer Society, and the AMGEN Award by the American Society of Biochemistry and Molecular Biology. He has been funded through three major grants from the National Institutes of Health, and National Cancer Institute. Recently, Shilatifard was selected as an inaugural recipient of the Outstanding Investigator Award from the National Cancer Institute and in 2016 he received the Walder Research Award from the Northwestern University. He serves as a Senior Editor for the journal Science, a Deputy Editor for Science Advances, Editor for Molecular and Cellular Biology, and also serves on the Scientific Advisory Boards of Genentech, and the Max Planck Society.

Hugh Taylor, M.D.
Yale University

Hugh Taylor, M.D., is the Anita O’Keeffe Young Professor of Women’s Health, and chair of the Department of Obstetrics, Gynecology, and Reproductive Science, at the Yale School of Medicine in New Haven, Connecticut. He is also professor of molecular, cellular, and developmental biology at Yale University, and chief of Obstetrics and Gynecology at Yale-New Haven Hospital. He is a board-certified specialist in obstetrics/gynecology and in reproductive endocrinology. Taylor received his undergraduate training at Yale University and received his medical degree from the University of Connecticut School of Medicine. He completed his
residency in obstetrics and gynecology at Yale University. His postdoctoral training included a fellowship in reproductive endocrinology and infertility as well as a fellowship in molecular biology, both at Yale University.

Taylor is a recipient of eight National Institutes of Health research grants and directs The Yale University Center for Reproductive Biology. His clinical research centers on implantation, endometriosis, and menopause. His basic science research focuses on uterine development, the regulation of developmental gene expression by sex steroids, endocrine disruption, and on stem cells. Taylor has published more than 300 articles in leading medical journals. He is the editor-in-chief of Reproductive Sciences, and an editor of Endocrinology.

He serves on several editorial boards and as a reviewer for numerous scientific journals and is frequently invited as a speaker at national and international medical meetings. Taylor has received numerous awards including the IVI Foundation International Award for the Best Research in Reproductive Medicine, and the Society for Gynecologic Investigation President Achievement Award. He has also served as the academic mentor of numerous trainees and has twelve times been awarded the Society of Gynecologic Investigation President Presenter’s Award for this training. Taylor is past president of the Society for Reproductive Investigation and was on the Board of Directors of The American Society for Reproductive Medicine, Environment & Human Health, and the International Institute of Primate Research. He was elected to the National Academy of Medicine in 2016.

Thea Tlsty, Ph.D.
University of California San Francisco

Shea Tlsty, Ph.D., is a professor in the Department of Pathology, and founding director of the Program in Cell Cycling and Signaling in the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco (UCSF), California. She received her doctorate from Washington University and trained at Stanford University before she was recruited to The University of North Carolina, Chapel Hill (UNC) as assistant professor of pathology and member of the UNC Lineberger Comprehensive Cancer Center. In 1994, she joined the faculty at UCSF where she is currently director of the Center for Translational Research in the Molecular Genetics of Cancer. She also serves as an Avon Scholar and Komen Scholar, studying breast cancer research. She regularly provides counsel to the National Institutes of Health. Tlsty studies genetic, epigenetic and functional changes involved in the earliest steps of cancer and how interactions between stromal components and epithelial cells collaborate to moderate carcinogenesis. Her research studies of human epithelial cells from healthy individuals are providing novel insights into how early molecular events affect genomic integrity and fuel carcinogenesis, tumor heterogeneity and malignant evolution. Prior work from her laboratory has shown that surrounding stroma can dramatically influence tumorigenesis both through signaling pathways and epigenetic reprogramming that have consequences for clinical disease. These studies provide novel insights into how early molecular events fuel cancer, tumor heterogeneity, and evolution.
Eric Tokar, Ph.D.
National Institute of Environmental Health Sciences

Erik J. Tokar, Ph.D., is the leader of the Stem Cell Toxicology Group in the National Toxicology Program Laboratory (NTPL) at the National Institute of Environmental Health Sciences/National Toxicology Program (NIEHS/NTP). His group investigates the roles of stem/progenitor cells in disease manifestation induced by exposure to environmental toxicants and works on NTPL mission-related projects that involve stem cells. The Group has mainly focused on the role of stem cells/cancer stem cells in inorganic carcinogenesis and has developed several animal and cell models that have helped discover and define mechanisms of action of these inorganics. The efforts of the Group also extend beyond cancer to include those diseases and conditions associated with exposure to NTP chemicals.

Paul Wade, Ph.D.
National Institute of Environmental Health Sciences

Paul A. Wade, Ph.D., is Acting Deputy Scientific Director, Deputy Chief of the Epigenetics and Stem Cell Biology Laboratory and head of the Eukaryotic Transcriptional Regulation Group. The group is interested in defining gene regulatory mechanisms and identifying key regulatory molecules with a focus on chromatin modification. Wade earned his doctorate in 1994 from Indiana University, Bloomington, Indiana and received postdoctoral training in the laboratory of the late Alan Wolffe at the National Institute of Child Health and Human Development. He has published more than 50 peer-reviewed articles in leading biomedical journals as well as several book chapters. He served as an Assistant Professor in the Department of Pathology and Laboratory Medicine at Emory University before joining NIEHS in October 2004.

Max Wicha, M.D.
University of Michigan

Wicha has been a major leader in the science of cancer stem cells. His group was part of the team that first identified breast cancer stem cells, the first such cells identified in solid tumors. His laboratory has identified a number of cancer stem cell markers, and developed in vitro and mouse models to isolate and characterize these cells, models which have been widely utilized in the field. His group has subsequently elucidated a number of intrinsic and extrinsic pathways which regulate stem cell self-renewal and cell fate decisions. This work has directly led to development of several clinical trials aimed at targeting breast cancer stem cells. According to the ISI citation index, Wicha is among the most highly cited investigators in the field of cancer stem cells. Wicha is also the founding director of the University of Michigan Comprehensive Cancer Center (UMCCC), a position he held for 27 years. Under his leadership, the UMCCC established itself as one of the nation’s premier cancer centers. In 2015, Wicha stepped down as the Cancer Center Director enabling him to devote his full efforts to cancer stem cell research. He now holds the Madeline and Sidney Forbes Professor of Oncology Chair and was
also recently appointed by President Obama to the National Cancer Advisory Board (NCAB). This board advises the National Cancer Institute Director and Secretary of Health on matters related to cancer research and health policy.

**Eda Yildirim, Ph.D.**
Duke University

Understanding epigenetic mechanisms, particularly those that are mediated by long noncoding RNAs is one of the two main research goals of Eda Yildirim, who joined Department of Cell Biology, at the Duke University School of Medicine, as an assistant professor, in August 2014. Yildirim uses mammalian X-chromosome inactivation as a model to study how IncRNA-mediated processes regulate gene expression, impact chromatin state, and participate in cell fate decisions during hematopoiesis. Her second interest is in understanding how spatial organization of the genome and gene expression is achieved through interactions that are formed between chromatin and components of the nuclear pore complex. Her lab approaches these questions by utilizing a variety of genetic, cell biological and genomics tools using mouse embryonic and adult (hematopoietic) stem cells and mouse models.

Yildirim’s interest in the epigenetic phenomena began when she was a doctoral student in Lutz Birnbaumer’s laboratory at University of California, Los Angeles studying calcium signaling in mammalian cells. She pursued this interest during her postdoctoral training with Jeannie Lee at Harvard Medical School/Massachusetts General Hospital where she focused on dissecting roles of IncRNA Xist and chromatin state in X chromosome dosage and understanding significance of these processes in cancer. By deleting the Xist locus in the hematopoietic stem cells of mice, Yildirim showed that Xist IncRNA is crucial for blood stem cell function and acts as a suppressor of cancer. This study provided the first direct and causal link between X chromosome dosage and cancer. Yildirim is a member of the Duke Cancer Institute, and is a recipient of several prestigious awards and fellowships including the Leukemia Research Foundation Hollis Brownstein Research Award (2015), Whitehead Scholars Award (2014), Massachusetts General Hospital Executive Committee on Research Medical Discovery Postdoctoral Award (2009), National institute of Health Fellows Award for Excellence (2006), and doctoral fellowship from the Higher Education Council of Turkey (1998). She received her Bachelor of Science with honors in Biology from Middle East Technical University in Ankara, Turkey (1997).

**Darryl Zeldin, M.D.**
NIEHS

Darryl C. Zeldin, M.D. is a Senior Investigator and the Scientific Director at the National Institute of Environmental Health Sciences, National Institutes of Health (NIEHS/NIH). He is an internationally recognized expert on eicosanoids (lipid mediators) and their role in regulating cardiovascular and respiratory function. Zeldin received his medical degree from Indiana University in 1986. He completed an Internal Medicine Residency at Duke University Medical
Center in 1989 and a Fellowship in Pulmonary/Critical Care Medicine at Vanderbilt University in 1993. He was recruited to the NIH in 1994 and promoted to Senior Investigator with Tenure in 2001. He directs a research program at NIH which involves both basic and clinical/translational studies. Zeldin is Board Certified in Internal Medicine and Pulmonary Medicine, is a Fellow in the American College of Chest Physicians, a Fellow in the American Heart Association and is an elected member of the American Society for Clinical Investigation and American Association of Physicians. Zeldin has co-authored over 300 primary peer-reviewed articles and his work has been cited over 20,000 times. His research has also been featured on NPR, Good Morning America, USA Today, US News and World Report, PBS, and on other nationally recognized media venues.

**Thomas Zwa**ka, M.D., Ph.D.
Icahn School of Medicine at Mount Sinai

Thomas Zwaka, M.D., Ph.D., research investigates how to direct pluripotent stem cells to replace diseased cells. He received his medical and doctoral degrees from Ulm University in Germany and his postdoctoral training in the lab of Jamie Thomson at the University of Wisconsin. In 2004, Zwaka joined the faculty of Baylor College of Medicine, serving in both the Department of Medicine and Cellular Biology and in the Center for Cell and Gene Therapy. Recruited by Mount Sinai in 2013 as a faculty member of the Icahn School of Medicine’s Department of Developmental & Regenerative Biology and the Black Family Stem Cell Institute, Zwaka established a novel collaborative effort designed to develop improved treatments for this neurodegenerative disease. He serves as the Editor-In-Chief of Stem Cell Research. Zwaka is the recipient of the 2009 Michael E. DeBakey, M.D., Excellence in Research Award.
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Cnot3 is required for male fertility and germline stem cell maintenance

Qing Chen, NIEHS
qing.chen3@nih.gov

Abstract:
The Ccr4-Not complex is the main deadenylase in eukaryotic cells, and it regulates mRNA poly(A)-tail length to influence mRNA stability and/or translation. We have previously shown that Ccr4-Not is required for embryonic stem cell (ESC) maintenance and poly(A) tail-length regulation serves as a critical post-transcriptional mechanism in the control of the pluripotent state. In addition to ESCs, multiple lines of evidence suggest that Ccr4-Not may also be involved in germ cell development. First, germ cells extensively rely on post-transcriptional gene regulation. Second, germ cells are considered to harbor latent pluripotency potential because they can re-acquire pluripotency via fertilization, teratocarcinogenesis, or spontaneous conversion during culture. Third, key germ cell factors (such as Nanos2) interact with Ccr4-Not in male germline stem cells. Therefore, we hypothesize that Ccr4-Not may play an important role in germ cell development, possibly in male germline stem cells. To test the hypothesis, we first examined the expression of Ccr4-Not subunits in adult testis. We found that the Cnot3 subunit is indeed highly enriched in male germline stem cells. We next generated a Cnot3 conditional knockout mice and derived the germline-specific deletion by breeding with the Vasa-CreERT2 strain. We found that germline-specific deletion of Cnot3 in males resulted in severe loss of germ cells and complete infertility. More importantly, careful examinations of neonatal males suggested that Cnot3 deletion led to specific loss of germline stem cells. Finally, to understand the underlying mechanism, we developed a novel technique to measure poly(A)-tail length of all detectable transcripts at the genomic scale. We are now using this technique to examine poly(A)-tail length changes after Cnot3 deletion in cultured germline stem cells. We are also carrying out RNA-seq and ribosome-profiling experiments to determine the impact of Cnot3 deletion on mRNA steady state level, stability, and translation efficiency. Together, our results will for the first time reveal the molecular mechanism of Ccr4-Not-dependent poly(A)-tail length regulation in germline stem cell maintenance and male germ cell development.

Contributing Authors:
Chen, Q, NIEHS
Wang, J, NIEHS
Lackford, B, NIEHS
Zheng, X, NIEHS
Hu, G, NIEHS
2. Identification of Nuclear Export Receptor CRM1 as a Novel Regulator of Developmental Genes in Embryonic Stem Cells

Amanda Conway, NIEHS
amanda.conway@nih.gov

Abstract:
Developmental genes mediate pattern formation and cell fate specification during the development of multicellular organisms. While precise regulation of developmental genes is critical for normal differentiation, deregulation of these genes can cause diseases such as cancer. Therefore, we sought to understand how developmental genes are dynamically and precisely regulated in embryonic stem cells (ESCs) and during differentiation. Here, we report a novel role for nuclear export receptor CRM1 in transcriptional regulation of developmental genes in ESCs. While CRM1 is known to mediate nucleocytoplasmic shuttling, its role on chromatin is less well understood. Using biochemical fractionations, we found that CRM1 localizes to chromatin in ESCs. To determine the genome-wide targets of CRM1, we performed ChIP-seq experiments using CRM1-specific antibodies. The majority of CRM1 peaks (80%) are located at the TSS or within gene bodies. Functional annotation of CRM1 target genes revealed strong association with developmental genes, specifically those encoding the homeodomain family of transcription factors. Correspondingly, CRM1 target genes are lowly expressed in ESCs and contain high levels of H3K27me3. Methylation of H3K27 is mediated by the Polycomb repressive complex (PRC2), and indeed, immunoprecipitation experiments confirm that CRM1 interacts with PRC2 members Jarid2, Suz12, Ezh2, and Eed. In addition to PRC2, we found that >85% of the CRM1 targets overlap with those of Erk2. Treatment of ESCs with an inhibitor of the Erk pathway demonstrated that active Erk2 is necessary for CRM1 and PRC2 enrichment on chromatin. Finally, we reactivated the Erk pathway and assessed the dynamics of CRM1 and Erk2 on chromatin at various time points. In conclusion, we elucidated the temporal regulation of developmental gene repression in ESCs following Erk activation and identified CRM1 as a novel regulator of PRC2-mediated gene silencing..

Contributing Authors:
Kumar, D, NIEHS
Yang, P, NIEHS
Kosak, J, NIEHS
Haldeman, J, Duke University
Cingu, S, NIEHS
Williams, S, NIEHS
Jothi, R, NIEHS
3. **Nickel Exposure Induces Persistent Epithelial-Mesenchymal Transition Through Epigenetic Reprogramming**

Suresh Cuddapah, *New York University School of Medicine*
suresh.cuddapah@nyumc.org

**Abstract:**
Nickel compounds are environmental carcinogens associated with the development of lung and nasal cancers in humans. Although Ni is a proven carcinogen, its mutagenic potential is low and the molecular basis of Ni-induced carcinogenicity is not fully understood. To gain insights into the molecular basis of nickel-exposure associated disease processes, we comprehensively analyzed Ni-induced alterations to the transcriptional program and chromatin modifications in immortalized non-cancerous human lung epithelial, BEAS-2B cells. Our results show that Ni exposure resulted in differential expression of several genes. While the transcriptional levels of several genes reverted to basal levels when the Ni-exposed cells were cultured without Ni for several generations (Ni-washed-out cells), a subset of genes remained differentially expressed. This suggests that Ni-exposure could elicit persistent changes to the transcriptional program. Analysis of the persistently differentially genes revealed epithelial-mesenchymal transition (EMT) to be the most activated biological process. Examination of mRNA and protein levels of epithelial and mesenchymal markers, as well as phenotypic characterization of the Ni-washed-out cells further confirmed acquisition of EMT phenotype. Since EMT process can contribute to disease conditions through its association with fibrosis and cancer progression, these results suggest the importance of Ni-induced persistent gene expression alterations in disease processes. Investigation of the epigenetic features of the differentially expressed genes in Ni-exposed and Ni-washed-out cells revealed stable alterations in histone modification profiles. This suggests epigenetic reprogramming as a basis for long-term gene expression alterations induced by Ni exposure.

**Contributing Authors:**
Jose, C, New York University
Tanwar, V, New York University
Jagannathan, L, New York University
Zhang, X, New York University
4. PM2.5 decreases endothelial progenitor cells through CARD9-mediated oxidative stress

Yuqi Cui, The Ohio State University
cui.69@osu.edu

Abstract:
Bone marrow derived endothelial progenitor cells (EPCs) play critical roles in angiogenesis and vascular functions. Fine particulate matter (PM) exposure significantly impairs cardiovascular functions and is closely associated with cardiovascular morbidity and mortality. Our previous study showed that PM exposure significantly decreased circulating EPC population via reactive oxygen species (ROS) formation. However, the detailed mechanisms are largely unknown. Caspase recruitment domain-containing protein 9 (CARD9) signaling is critically involved in the innate immune response via activation of pro-inflammatory cytokines as well as ROS generation. The present study aimed to determine if PM-induced inflammation and ROS formation was through activation of CARD9 pathway. Both male wild-type (WT) C57BL/6 mice (8-10 weeks) and age-matched CARD9 knockout (KO) mice (with C57BL/6 background) were exposed to PM2.5 for 6 weeks via intranasal approach with PBS as the control. Serum concentrations of the cytokines including IL-6, IL-1β, and TNF-α were measured with ELISA in the mice before and after PM exposure. Blood cells were collected and prepared for EPC analysis using flow cytometry. There was no difference in the serum levels of IL-6, IL-1β, and TNF-α; or TNF-α between WT mice and CARD9 KO mice exposed to PBS. As expected, PM exposure substantially increased the serum levels of IL-6, IL-1β, and TNF-α; in the WT mice (by up to 6 times) in association with significantly increased intracellular ROS production and decreased level of circulating CD34+/CD133+ cell population (EPCs). However, no significant increase in the serum concentrations for IL-6, IL-1β, and TNF-α was observed in CARD9 KO mice exposed to PM without significant changes in the intracellular ROS formation and the level of circulating CD34+/CD133+ cell population. In conclusion, the present study demonstrated that a significant amount of cytokines were produced in WT mice in association with significantly increased intracellular ROS and decreased circulating EPCs, but not in CARD9 KO mice with PM exposure. The data suggested that PM2.5 exposure attenuated circulating EPC population mainly through CARD9-mediated oxidative stress largely due to production of inflammatory cytokines and ROS formation.

Contributing Authors:
Cui, Y, The Ohio State University
Liu, X, The Ohio State University
Xiao, Y, The Ohio State University
Zhu, Q, The Ohio State University
Jiang, M, The Ohio State University
Hao, H, The Ohio State University
Abraham, J, The Ohio State University
Jiang, B, The Ohio State University
Sun, Q, The Ohio State University
Liu, Z, The Ohio State University
Abstract:
In the 1970’s, Michigan residents were exposed to an industrial mixture of polybrominated biphenyl (PBBs), an endocrine-disrupting compound, when it was added to farm animal feed during a factory accident. Exposed individuals and their children have numerous health problems, though the underlying mechanism behind these health problems remains unknown. Other endocrine-disrupting compounds have been linked to epigenetic differences, but no epigenetic studies have been done for PBB. Therefore, DNA from the blood of individuals with current (N = 651) PBB-153 levels (the majority congener in the industrial mixture of PBBs) was interrogated with the MethylationEPIC BeadChip. Associations between each of the ~850,000 CpG sites and serum PBB levels were tested with a linear regression that controlled for age, sex, and cell type proportion. After multiple test correction (FDR <0.05), 1821 CpG sites associate with current PBB-153 levels. A subset of this cohort (N=63) also had detectable exposure to other PBB congeners (PBB-101 and PBB-77). Using this information, a total PBB exposure level was calculated and associated with 76 significant CpGs. The CpGs that are associated with PBB exposure are in genes that are associated with proper development and hormone signaling, as well as being important for proper gene regulation and cell growth in adults. For example, CpGs in RAMP3, a gene needed for adrenomedullin hormone signaling, associate with PBB-153 (p = 1.67E-07) and total PBB (p = 3.26E-06) levels. Follow-up analyses suggested that many of the observed associations were driven by a small group of highly exposed individuals. Further work will investigate differences between these and other highly exposed individuals, and assess whether these CpG sites associate with the development of health problems in exposed individuals.

Contributing Authors:
Kilaru, V, Emory University
Terrell, M, Emory University
Marcus, M, Emory University
Conneely, K, Emory University
Smith, A, Emory University
6. Hexavalent Chromium Exposure Leads to Trans-Generational Developmental Defects and Cancer Predisposition

Vamsi Gangaraju, *Medical University of South Carolina*  
gangaraj@musc.edu

**Abstract:**  
Hexavalent chromium - Cr(VI) is one of the most mutagenic environmental toxicants with direct links to cancer. Evidence suggests that Cr(VI) exposure leads to teratogenic effects in mammals. It is therefore of utmost importance that we unravel the mechanistic basis for Cr(VI) exposure dependent trans-generational effects. Effect of Cr(VI) exposure on the exposed individual is well documented; however, teratogenic effects of Cr(VI) are poorly elucidated and mechanistic basis of the same remains elusive. This is partly due to the absence of a reliable, genetically tractable model system that is conducive for multi-generation studies. We introduce Drosophila as the model system to study teratogenic effects of parental exposure to Cr(VI). Our preliminary data shows that Cr(VI) exposure of Drosophila - a) leads to the deposition of Cr in the ovary, b) leads to phenotypic variations in the progeny, c) shows that phenotypic variations are not dependent on genetic mutations but are due to epigenetic mechanisms, d) shows that TGFβ ligand Daw is a bonafide downstream effector of Cr(VI) exposure and RNAi knock down of Daw mRNA leads to rescue of phenotypic variations, e) Cr(VI) exposure leads to cancer phenotypes in the progeny and f) Cr(VI) exposure dependent propensity to induce cancer phenotypes in the progeny is fixed in the population for at least three generations. These studies thus establish a mechanistic basis for Cr(VI) exposure dependent trans-generational cancer predisposition.

**Contributing Authors:**  
Parikh, R, Medical University of South Carolina  
Hazard, S, Medical University of South Carolina  
Zhong, M, New York University  
Hardiman, G, Medical University of South Carolina  
Chen, L, New York University  
Gangaraju, V, Medical University of South Carolina
7. Lipidome Profiles are Related to Preterm Birth in African American Women

Carmen Giurgescu, *The Ohio State University*  
*giurgescu.1@osu.edu*

**Abstract:**  
African American women are more likely to live in disadvantaged neighborhoods (e.g., disorder, violent crime), to experience higher levels of perceived stress and depressive symptoms, and to have preterm birth (less than completed 37 weeks gestation) compared with non-Hispanic white women. Disadvantaged neighborhoods, perceived stress and depressive symptoms have been related to higher risk of preterm birth. Limited data also suggest that lipidome profiles [e.g., omega(n)-3 PUFA, n-6 PUFA] are altered for pregnant women with higher levels of depressive symptoms and women with preterm birth. The goal of this study was to explore if a lipidome profile is related to disadvantaged neighborhoods, perceived stress, depressive symptoms and preterm birth. A sample of 38 pregnant African American women participated in this pilot study. Eight women had preterm birth. Women completed questionnaires and had blood drawn in the 2nd trimester of pregnancy. Plasma lipidome profiles were determined by “shotgun” high resolution/accurate mass spectrometry. Birth data were collected from medical records. Women who reported higher levels of neighborhood disorder also reported higher levels of perceived stress (p<.05). Higher levels of perceived stress were related to higher risk of preterm birth (p<.05). Compared with women with term birth, women with preterm birth had had lower levels of GPSer-44:09 (glycerophosphoserine) and DG (40:4) (diacylglycerols) when controlling for maternal age and medical history (e.g., hypertensive disorders). Disadvantaged neighborhoods and depressive symptoms were not related to lipidome profiles. The high preterm birth rate for African American women has persisted for decades, pointing to the need for new approaches. Lipidomics is a tool for discovery of potential novel biomarkers for preterm birth research.

**Contributing Authors:**  
Misra, D.P, Wayne State University  
Lydic, T, Michigan State University  
Podolsky, R, Wayne State University  
Stemmer, P, Wayne State University  
Dailey, R, Wayne State University
8. Development of a Novel Cell-Tracking Strategy in Bone Regenerative Devices

Han Han, University of North Carolina at Chapel Hill
han88@email.unc.edu

Abstract:
Objectives: Cell-based graft devices (CBGD) are usually composed of two major components: supporting scaffolds and functionally active cells to regenerate biologically functional tissues. CBGD have been shown to advance bone tissue engineering and overcome limitations that only use synthetic substitutes in the treatment of oral and craniofacial defects. However, current techniques using fluorescent probes fail to sufficiently monitor the viability and function of transplanted cells in vivo, which limits CBGD’s evolvement. To more accurately monitor transplanted cells in a spatiotemporal manner, we hypothesized that utilizing eGFP-NanoLuc (GpNLuc), a fusion reporter which generates the brightest bioluminescent signal known to date from the intra-molecular bioluminescence resonance energy transfer between NanoLuc and eGFP, will overcome the problems associated with traditional fluorescent probes and enable real-time tracking of cell viability, location, and function. Methods: Stable-transfection of GpNLuc in rat mesenchymal stem cells (rMSC) was developed and a series of in vitro assays including MTT assays and analysis of rMSC differentiation together with animal studies were performed to prove the concept that GpNLuc does not alter the physiological characteristics of rMSC but can efficiently monitor transplanted cells in live animals. Moreover, the GpNLuc stable cells were further tested in a 3D scaffold composite to assess cell growth. Results: GpNLuc did not significantly affect cell viability/proliferation (p>0.05) and the capability of adipogenic, chondrogenic and osteogenic differentiation in rMSCs. Furthermore, GpNLuc was successfully applied to quantify cell number and could generate an intense bioluminescent emission suitable for detecting and tracking rMSCs the host skin temporally and non-invasively. Local eGFP excitation enables improved sensitivity of GpNLuc by avoiding interference created by surrounding tissue or the 3D scaffold auto-fluoroscence resulting from traditional ectopic excitation. Conclusions: We have developed an innovative cell tracking strategy to better understand the biology of transplanted cell migration and function during tissue regeneration at an injury site. KEYWORDS: Cell-tracking, Reporter, Graft devices, Bone Regenerative, Stem cell, bioluminescent. Supported by NIH/NIDCR R01DE022816-01.

Contributing Authors:
Han, H, University of North Carolina at Chapel Hill, & Sichuan University, China
Huang, B, University of North Carolina at Chapel Hill
Lee, D, University of North Carolina at Chapel Hill
Zhao, L, University of North Carolina at Chapel Hill, & Sichuan University, China
Amelio, A.L, University of North Carolina at Chapel Hill
Ko, C, University of North Carolina at Chapel Hill
9. Toxicogenomic Profiling of Human Embryonic Stem Cells Exposed to a Panel of Epigenotoxicants - Preliminary Observations

Cheryl Hobbs, *ILS, Inc.*
chobbs@ils-inc.com

**Abstract:**
Disruption of the epigenetic circuitry in stem cells by exposure to drugs and environmental chemicals can lead to developmental defects and adverse health effects. A biomarker panel capable of detecting a chemical’s potential to alter the stem cell epigenome (“epigenotoxicant”) should have utility for hazard identification. We are developing a gene signature capable of detecting chemicals that modulate histone methylation or acetylation in human pluripotent embryonic stem (hES) cells. H9 hES cells were exposed to multiple concentrations of a panel of ~60 chemicals representative of different classes of chemical inhibitors and activators of histone methylation or acetylation. Cells were exposed to chemicals for 24 hours prior to harvest to minimize potentially confounding effects of spontaneous gene expression changes. RNA isolated from cells exposed to ~IC0-10 and ~IC30-50 concentrations of 24 chemicals was sequenced to date by RNA-Seq (n=3). Preliminary transcriptome profiling detected genes in the “transcriptional regulator network in embryonic stem cells” pathway that are frequently dysregulated in a directionally conserved manner in response to treatment with histone methyltransferase (HMT), acetyltransferase (HAT) and deacetylase (HDAC) inhibitors, and to a lesser extent, putative non-epigenotoxicants, at IC30-50 concentrations. This suggests that diverse mechanisms of toxicity may converge on this network of genes that are important for regulating stem cell pluripotency and development. Bioinformatic pathway analyses revealed considerable overlap in the canonical pathways and biological functions most affected by the various chemical classes. These include a variety of signaling pathways and processes related to death, cell survival, neuronal development and cancer. Comparison of differentially expressed genes (DEGs) for the HMT, HAT and HDAC inhibitor classes identified 445, 754 and 3141 shared genes, respectively; a subset of 191 DEGs common to all the tested chemicals in these three classes was also identified, further implying that these chemicals affect some mutual pathways and genes. Although bioinformatics using more chemicals in conjunction with chromatin immunoprecipitation is needed to derive a gene panel specific for effects on the histone code rather than general toxicity, these results suggest that this toxicogenomic approach may lead to a predictive signature of epigenotoxicity in human stem cells. (Supported by NIEHS: 2R44ES023526-02).

**Contributing Authors:**
Sinha, N, ILS, Inc.           Gagne, R, Health Canada
Christy, N, ILS, Inc.         Williams, A, Health Canada
Morton, B, ILS, Inc.          Recio, L, ILS, Inc.
Chepelev, N, Health Canada
10. Chromatin Dependent Glucocorticoid Receptor Plasticity Within the Cancer Genome

Jackson Hoffman, NIEHS
jackson.hoffman@nih.gov

Abstract:
Upon hormone stimulus, type I nuclear receptors (NRs) bind to their hormone ligand, enter the nucleus, and interact with regulatory elements in the DNA to elicit changes in transcriptional activity. NRs are required throughout development and in adult life, and NR activities are frequently targeted in the treatment of human diseases. Activation of Glucocorticoid Receptor (GR) with the synthetic corticosteroid dexamethasone is commonly used to promote fetal lung development and to combat auto-immune and inflammatory disorders. Elucidating the genetic and transcriptional mechanisms by which GR and other NRs perform their myriad functions is critical for human health and disease treatment. Brg1, the catalytic ATPase of the human SWI/SNF complex, is critical for hormone-induced transcriptional regulation by GR. Previous studies from our lab demonstrated that upon DNA-binding, GR recruits Brg1 to remodel the local chromatin architecture to alter transcriptional output. Our work significantly expands this model and suggests that Brg1 may act on hormone-regulated genes prior to hormone stimulus and GR binding. Using ChIP-seq, we have generated a genome-wide map of Brg1 and GR chromatin interactions in untreated and dexamethasone-treated cells. We show that Brg1 interacts with many GR binding sites in untreated cells and is present at these sites upon dexamethasone treatment and subsequent GR binding. Using these and other data sets, we have identified three classes of GR binding sites that are differentially associated with hormone-dependent transcriptional events. These classes of binding site showed distinct patterns of chromatin accessibility, histone modification, and transcription factor binding. Examination of GR binding in Brg1-deficient cells revealed that disruption and restoration of Brg1 expression selectively alters the chromatin environment at these classes of GR binding sites. Taken together, these data suggest that GR elicits the transcriptional response to hormone via multiple distinct mechanisms that are dependent on specialized chromatin environments. Our classification of these genomic environments provides a more profound understanding of nuclear receptor function that will allow new approaches in drug development and disease treatment..

Contributing Authors:
Trotter, K, NIEHS
Archer, T, NIEHS
11. Role of the non-catalytic SWI/SNF Subunit BAF155 in hESC Differentiation

Lee Langer, NIEHS
lee.langer@nih.gov

Abstract:
The multi-subunit SWI/SNF chromatin-remodeling complex is a major epigenetic regulator in human embryonic stem cells (hESCs), and its loss of function has been shown to lead to differentiation. However, different subunits of this large complex have variable effects on stem cell pluripotency, and the specific functions of each subunit are unknown. We therefore generated hESC lines expressing doxycycline-inducible shRNAs against several SWI/SNF complex members, including BAF155 and the catalytic subunit BRG1, and subjected the cells to NanoString analysis and an embryoid body (EB) differentiation protocol. NanoString analysis of BAF155 and BRG1 KD cells revealed the altered expression of several transcripts known to be involved in mediating pluripotency and differentiation. Notably, several of the genes affected in the BAF155 KD condition were not altered following BRG1 KD, suggesting potential SWI/SNF-independent actions of BAF155 on hESC biology. To further explore these effects, BAF155 KD and BRG1 KD cells were subjected to an EB assay in which cells are allowed to differentiate in a non-directed manner over 12 days. NanoString analysis was performed using these EBs, and data clustering showed that BAF155 KD EBs exhibited a different transcriptional response than those expressing lower levels of BRG1. Notably, this effect was observed at both Day 5 and Day 12 of the EB assay. These results reveal that the loss of BAF155 expression has differential effects on the transcriptional response of hESCs compared to BRG1 KD in both steady state and differentiation conditions. The data therefore suggest that BAF155 plays a previously unappreciated role in hESC lineage choice. To understand these results at a more mechanistic level, ATAC-seq will be performed using BAF155 and BRG1 KD cells, and the effects of these manipulations on chromatin accessibility will be examined. In combination with directed differentiation assays, these analyses will further illuminate the role of BAF155 specifically, and chromatin modifying complexes in general, in the regulation of hESC differentiation.

Contributing Authors:
Langer, L, NIEHS
Park, S, Washington University
Ward, J, NIEHS
Archer, T, NIEHS
12. ORIO (Online Resource for Integrative Omics): a web-based platform for rapid integration of next generation sequencing data

Christopher A. Lavender, NIEHS
Christopher.lavender@nih.gov

Abstract:
Established and emerging next generation sequencing (NGS)-based technologies allow for genome-wide interrogation of diverse biological processes. However, accessibility of NGS data remains a problem, and few user-friendly resources exist for integrative analysis of NGS data from different sources and experimental techniques. Here, we present Online Resource for Integrative Omics (ORIO; https://orio.niehs.nih.gov/), a web-based resource with an intuitive user interface for rapid analysis and integration of NGS data. To use ORIO, the user specifies NGS data of interest along with a list of genomic coordinates. Genomic coordinates may be biologically relevant features from a variety of sources, such as ChIP-seq peaks for a given protein or transcription start sites from known gene models. ORIO first iteratively finds read coverage values at each genomic feature for each NGS dataset. Data are then integrated using clustering-based approaches, giving hierarchical relationships across NGS datasets and separating individual genomic features into groups. In focusing its analysis on read coverage, ORIO makes limited assumptions about the analyzed data; this allows the tool to be applied across data from a variety of experiments and techniques. Results from analysis are presented in dynamic displays alongside user-controlled statistical tests, supporting rapid statistical validation of observed results. We emphasize the versatility of ORIO through diverse examples, ranging from NGS data quality control to characterization of enhancer regions and integration of gene expression information. Easily accessible on a public web server, we anticipate wide use of ORIO in genome-wide investigations by life scientists.

Contributing Authors:
Shapiro A, NIEHS
Burkholder A, NIEHS
Bennett B, NIEHS
Adelman K, Harvard Medical School
Fargo D, NIEHS
13. Sex Differences in Genotoxic and Epigenotoxic Effects of 1,3-Butadiene in Mice

Lauren Lewis, Texas A&M University
llewis@cvm.tamu.edu

Abstract:
1,3-Butadiene (BD) is a widely used industrial chemical and ubiquitous environmental contaminant. Although genotoxicity is an established mechanism of BD carcinogenicity, it does not explain the tissue-specific tumorigenicity observed in mice. Previous studies have shown that epigenetic alterations may contribute to tissue-specific toxicity in mice exposed to BD. In the present study, we investigated whether or not the epigenetic effects of BD are also sex-specific. We tested the hypothesis that short term exposure to BD will result in sex-specific effects on the epigenome. BD genotoxicity and epigenotoxicity were evaluated in both male and female mice in liver, lung, and kidney tissues. Female and male C57BL/6J, A/J and CAST/EiJ mice were exposed to 0 or 425 ppm of BD by inhalation (6 hr/day, 5 days/week) for 2 weeks. Genotoxicity was evaluated by measuring THB-Gua adducts and bis-N7G-BD crosslinks. We observed that exposure to BD resulted in similar levels of THB-Gua adducts and bis-N7G-BD crosslinks in liver, lung, and kidney tissues in male and female mice. In order to investigate the epigenetic effects, histone modifications were analyzed. Specifically, trimethylation of histones H3K9, H3K27, and H4K20, all marks of condensed heterochromatin, exhibited differences between sexes in the kidneys and livers of BD-exposed mice. The presence of sex differences in histone lysine methylation levels and DNA damage prompted further investigation of gene expression levels of histone and DNA methyltransferases along with DNA repair enzymes. In liver tissue, DNA repair as well as histone and DNA methyltransferase gene expression was downregulated after BD exposure in both male and female mice. We conclude that BD effects on the epigenome are sex-specific.

Contributing Authors:
Chappell, G, University of North Carolina
O’Brien, B, University of North Carolina
Kobets, T, University of North Carolina
Tretyakova, N, University of Minnesota
Sangaraju, D, University of Minnesota
Kosyk, O, University of North Carolina
Sexton, K, University of North Carolina
Bodnar, W, University of North Carolina
Pogribny, I, U.S. Food and Drug Administration
Rusyn, I, Texas A&M University
14. Rif1 Promotes a Repressive Chromatin State to Safeguard Against Endogenous Retrovirus Activation

Pishun Li, NIEHS
pishun.li@nih.gov

Abstract:
Transposable elements, including endogenous retroviruses (ERVs), constitute a large fraction of the mammalian genome. They are transcriptionally silenced during early development to protect genome integrity and aberrant transcription. However, the mechanisms that control their repression are not fully understood. To systematically study ERV repression, we carried out an RNAi screen in mouse embryonic stem cells (ESCs) and identified a list of novel regulators. Among the identified factors, Rif1 displays the strongest effect. Rif1 depletion by RNAi or gene deletion led to increased transcription and increased chromatin accessibility at ERV regions and their neighboring genes. This transcriptional de-repression is more severe when Rif1 is silenced in ESCs devoid of DNA methylation. Mechanistically, Rif1 directly occupies ERVs and is required for repressive histone mark H3K9me3 and H3K27me3 assembly and DNA methylation. It interacts with histone methyltransferases (HMTs) and facilitates their recruitment to ERV regions. Finally, Rif1 acts as a barrier during somatic cell reprogramming, and its depletion significantly enhances reprogramming efficiency. Together, our study uncovered many previously uncharacterized repressors of ERVs, and defined an essential role of Rif1 in the epigenetic defense against ERV activation.

Contributing Authors:
Wang, L, NIEHS
Bennet, B, NIEHS
Wang, J, NIEHS
Qin, Y, NIEHS
Takaku, M, NIEHS
Li, J, East China Normal University
Wade, P, NIEHS
Wong, J, East China Normal University
Hu, G, NIEHS
15. In Utero Exposure to Bisphenol A Induces Mammary Epithelial Cell Reprogramming in MMTV-ErbB2 Transgenic Mice

Amanda Parris, North Carolina Central University
ablack18@nccu.edu

Abstract:
Nearly 95% of the United States population has been exposed to Bisphenol A (BPA), a component of polycarbonate plastics that is detected in many household items. As an endocrine disrupting compound, BPA elicits pro-estrogenic effects, which can have major health implications. In particular, in utero exposure to BPA (IUE BPA) has been associated with modified mammary development in preclinical models. However, BPA-induced changes in molecular signaling and mammary epithelial cell (MEC) developmental dynamics remain unclear. Although it is generally believed that the modulation of mammary stem cells (MaSCs) is involved in these processes, supporting evidence from in vivo models is lacking. Building on previous data suggesting that IUE BPA promotes mammary tumorigenesis, our current study aimed to investigate the effects of IUE BPA on mammary development in MMTV-ErbB2 transgenic mice with particular emphasis on MEC population changes. Pregnant MMTV-ErbB2 mice were administered BPA (12.5 and 25 µg/L) in the drinking water daily from gestational day 13-19. This method of IUE BPA recapitulates the primary route of human exposures (through food/water consumption). At 6 and 10 weeks of age, whole mount analyses showed that mammary glands of mice in the low-dose IUE BPA group had increased ductal elongation and density as compared to the control mice, which indicates the promotion of mammary development. To understand how IUE BPA promotes mammary morphogenesis, we performed flow cytometry analysis of MEC subpopulations in control and IUE BPA mice. Using CD24/CD49f cell markers, we found that IUE BPA altered the relative composition of luminal and basal cell populations. Importantly, IUE BPA increased the CD24+CD49f+ mammary reconstituting unit (MRU) subpopulation of MECs, which is enriched with MaSCs. Together, our MEC population data suggest that IUE BPA induces MEC reprogramming. Low-dose IUE BPA also increased colony formation, self-renewal, and anchorage-independent cell growth of the MECs as measured by functional stem cell assays, including colony-forming cell, mammosphere, and 3D culture assays, respectively. Molecular analysis of mammary tissues further indicated that IUE BPA induced concurrent activation of growth factor and estrogen receptor pathways. Our data showed the effects of IUE BPA on MaSCs during peripubertal mammary development and highlighted the morphogenic and functional consequences that are associated with increased mammary tumor risk.

Contributing Authors:
Zhao, Q, North Carolina Central University
Howard, E, North Carolina Central University
Ma, Z, North Carolina Central University
Liu, Y, North Carolina Central University
Yang, X, North Carolina Central University
16. Transcriptomics profiling of human embryonic H9 cells to evaluate relative potency and modes of action of selected flame retardants

Leslie Recio, *ILS, Inc.*
lrecio@ils-inc.com

**Abstract:**
Bisphenols are widely used chemicals that are present in consumer products either as plasticizers or as flame retardants. As a consequence, human exposure to these chemicals is ubiquitous. Bisphenol A (BPA) is associated with numerous adverse health outcomes. This prompted its removal from many products and replacement with other bisphenol analogs, such as BPS, and BPF amongst others. In addition, otherbisphenols such as 3,3’,5,5’-Tetrabromo BPA have been used as flame retardants. The toxicity of BPA has been widely studied; however, the effects of the other bisphenols are less known. Our studies have shown that BPS, for example, has endocrine disrupting properties similarly to BPA. Many of these chemicals, including BPA, have been shown to have developmental effects. Therefore, we used H9 human embryonic stem cells (hESC; WA09) to investigate toxicity to this vulnerable cell population. We hypothesized that exposure of H9 cells to bisphenols will result in perturbation of gene expression and signaling pathways that are indicative of toxicological hazards that impact embryonic stem cells. Dose response experiments were conducted on H9 hESCs using four chemicals: 3,3’,5,5’-Tetrabromobisphenol A (500-700 μM; TBPA), BPA (200-250 μM), BPF (250-400 μM), and BPS (300-500μM). Cytotoxicity curves were generated and non-cytotoxic concentrations were used for NGS. Total RNA was collected, ribodepletion-based next-generation sequencing (NGS) was used to identify differentially expressed genes (DEGs), upstream regulators, and cellular signaling pathways that could be relevant to the toxicity of the four compounds. Functional analysis of DEGs was undertaken in Ingenuity Pathway Analysis (IPA). All bisphenols perturbed a large number of genes in a dose-dependent manner. Analysis in IPA revealed similarities as well as differences in canonical pathways and upstream regulators in response to TBPA, BPA, BPF, and BPS. Benchmark dose modeling of these transcriptomics data aligned well with differential cytotoxicity and may provide a useful basis for relative potency ranking of the compounds. Taken together, toxicological hazards could be identified in this model system in response to BPA and its analogues, suggesting potential impacts on embryonic stem cells.

**Contributing Authors:**
Peshdary, V, Health Canada
Chepelev, N, Health Canada
Gagné, R, Health Canada
Maynor, T, ILS, Inc.
Yauk, C, Health Canada
Atlas, E, Health Canada
17. Multi-generational Impacts of Arsenic Exposure on DNA Methylation and Their Implication In Arsenic Carcinogenesis

Xuefeng Ren, University at Buffalo
xuefengr@buffalo.edu

Abstract:
Exposure to arsenic, an established human carcinogen, is a significant global public health concern. Increasing evidence has suggested that arsenic is a strong regulator of the epigenome, i.e. DNA methylation. However, evidence from human studies particularly is lacking in our understanding the impact of timing of arsenic exposure (adulthood, in utero or germline) on DNA methylation patterns, and the carcinogenic relevance of arsenic-induced aberrant DNA methylation. To shed lights on these questions, we performed a pilot family-based study in Hetao Plain in Inner Mongolia, China, where the changes of drinking water sources in past decades created a unique arsenic exposure scenario among families living in this region: grandparents, parents and grandchildren living in the same family were exposed to arsenic in adulthood, in utero/early childhood, and in germline, respectively. In this pilot study, we analyzed 18 exposed families vs. 9 control families vs. 18 arsenicosis/skin cancer patients; genome-wide DNA methylation profiling indicated significant overlap of genomic loci with altered DNA methylation levels across generations (i.e., common methylation alterations present despite differences in timing of arsenic exposure). Moreover, significantly more genomic loci were differentially methylated in the parent generation, indicating that early life exposure (in utero/early childhood) may be more susceptible to arsenic-induced DNA methylation alterations. Lastly, a set of differentially methylated loci (DMLs) and genomic regions (DMRs) were manifested in arsenicosis/skin cancer patients. Together, it suggests that arsenic exposure disrupts global DNA methylation and leaves traceable aberrant DNA methylation marks even if exposure being stopped decades ago, which persists and can be identified across multiple generations and are enriched in people with a higher risk for arsenic-induced toxicity and carcinogenesis.

Contributing Authors:
Chen, X, University at Buffalo
Guo, X, Wenzhou Medical University, China
Gaile, D, University at Buffalo
Wang, J, University at Buffalo
Liu, Z, Inner Mongolia Medical University, China
Wu, H, Wenzhou Medical University, China
Ren, X, University at Buffalo
18. Exposure of embryonic rat cortical neurons to BDE-47 hydroxylated metabolite 6OH-BDE-47 disrupts neuronal maturation and function by epigenetic mechanisms

Ramendra Saha, University of California, Merced
rsaha3@ncmerced.edu

Abstract:
Polybrominated diphenyl ethers are an environmentally pervasive class of brominated flame retardants found at especially high levels in households in the United States. Their environmental stability, propensity for bioaccumulation, and known potential for neurotoxicity has led to much research focusing on their effects on the developing nervous system and association with neurodevelopmental disorders. Despite this effort, a complete understanding of their causal role in such disorders has not been achieved, as little is yet understood concerning how the mechanisms of their toxicity relate to observed associations with developmental disruption. Here, we report the effects of one of the most prevalent congeners, BDE-47, and its hydroxylated metabolites on the maturation and function of embryonic rat cortical neurons. We have found that exposure to the hydroxylated metabolite, 6OH-BDE-47, exhibits the strongest effects, including: disruption of activity-induced gene transcription, widespread dysregulation of mRNA levels of genes associated with neurodevelopmental disorders, and, intriguingly, expression of a critical subunit of the BAF chromatin remodeling complex, BAF170. Interestingly, the observed effects appear to be mediated apart from disruption of thyroid hormone signaling, perhaps instead via exerting influence on epigenetic regulation. Results from this study have identified a novel aspect of 6OH-BDE-47 toxicity and allowed us to explore the effects of an environmental challenge on BAF-related regulation of neuronal maturation and activity induced transcription of immediate early genes.

Contributing authors:
Poston, R, University of California, Merced
Dunn, C, University of California, Merced
Sarkar, P, University of California, Merced
19. Mutations in SMCHD1 are Associated With Congenital Arhinia and Facioscapulohumeral Muscular Dystrophy Type 2

Natalie Shaw, NIEHS
natalie.shaw@nih.gov

Abstract:
Arhinia (absent nose) is a rare congenital malformation frequently associated with ocular and neuro-reproductive defects. The genetic cause is unknown. We assembled a cohort of 40 patients with arhinia and used next generation sequencing and functional modeling to identify the etiology of this disorder. We identified rare, heterozygous missense SMCHD1 variants in 86% of cases. All variants were located in the SMCHD1 ATPase domain which we determined to be under strong evolutionary constraint. Gene-based burden testing of rare variants confirmed that SMCHD1 was the only gene to achieve genome-wide significance (p=2.9x10^-17). This discovery was unexpected as loss-of-function mutations in SMCHD1, in combination with a permissive D4Z4 haplotype, cause a rare form of muscular dystrophy (FSHD2). SMCHD1 is an epigenetic repressor that silences X-chromosome and autosomal genes. In FSHD2, loss of SMCHD1 function leads to D4Z4 hypomethylation and abnormal expression of the muscle toxin, DUX4. Variants associated with FSHD2 span the entire gene and include missense and truncating mutations; variants associated with arhinia were exclusively missense and within the ATPase domain. However, several FSHD2-specific mutations also localized to the ATPase domain, and at least 3 FSHD2 variants were detected in our arhinia cohort. The arhinia mutations had the same direction of effect as reported for FSHD2 mutations: 74% of arhinia cases with an SMCHD1 variant had D4Z4 hypomethylation characteristic of FSHD2 while family members without an SMCHD1 variant did not. Further analyses identified two arhinia patients and a father who met all genetic requirements for FSHD2; one patient has asymmetric muscle atrophy and the father is being treated for muscular dystrophy. SMCHD1 suppression in zebrafish caused abnormal facial cartilage, small eyes, and blunted GnRH-immunopositive terminal nerve projections. Each phenotype was rescuable with wild-type but not with mutant SMCHD1 mRNA, demonstrating assay specificity. RNAseq and gene-set analyses in human cell lines revealed down-regulation of genes statistically enriched for one phenotype: - depressed nasal tip. Rare variants in an evolutionarily constrained region of SMCHD1 are associated with arhinia. Mutations in SMCHD1 also cause an oligogenic form of muscular dystrophy, demonstrating a strikingly diverse phenotypic spectrum from identical alleles and implicating disruption of critical interactions with other loci.

Contributing Authors:
Brand, H, Massachusetts General Hospital
Kupchinsky, Z, Duke University
Graham, J, Cedars Sinai Medical Center
Lin, A, Massachusetts General Hospital
Katsani, N, Duke University
Crowley, W, Massachusetts General Hospital
FitzPatrick, D, University of Edinburgh
Davis, E, Duke University
Talkowski, M, Massachusetts General Hospital
20. Genetic Model of GATA3 Mutation Reveals Tumor-Promoting Functions of ZnFn2 GATA3 Mutations in Breast Cancer

Motoki Takaku, NIEHS
motoki.takaku@nih.gov

Abstract:
A pioneer transcription factor, GATA3, is one of the most frequently mutated genes in breast cancer. Based on the Cancer Genome Atlas (TCGA) data cohort, more than 10% of breast tumors harbor somatic mutations in this gene, and over 90% of these mutations are observed within the luminal subtypes of breast cancer. GATA3 expression has been thought to be a promising prognostic marker for breast cancers, as its expression highly correlates with the expression level of ERalpha. However, clinical and biological impacts of GATA3 mutations are largely unknown. We have developed a novel strategy to classify GATA3 mutations into 5 groups based on the locations and resulting protein products: (1) ZnFn2 mutations, (2) splice site mutations, (3) truncation mutations, (4) extension mutations, and (5) missense mutations. This novel classification revealed distinct clinical properties of each mutation group. In particular, the patients bearing tumors that carry mutations in the second GATA3 zinc-finger motif (ZnFn2) were unique, as they were associated with luminal B subtype and worse prognosis. To investigate the molecular outcomes induced by ZnFn2 mutations, we utilized the CRISPR-Cas9 system and generated a breast cancer cell line, which expresses a ZnFn2 mutant (R330fs) endogenously. A two-nucleotide deletion from the single allele had surprisingly large effects on breast cancer properties. The ZnFn2 mutant cell line manifested increased tumor growth as xenografts, more aggressive phenotypes in vitro, and chromatin reprogramming including mislocalization of luminal transcription factors, GATA3, ERalpha and FOXA1. The resulting reprogrammed transcriptome is characterized by a significant reduction in progesterone receptor expression, which facilitates the acquisition of a growth advantage following progesterone treatment. Our results are the first demonstration of tumor-promoting functions of specific GATA3 mutations in breast cancer. These mutations may also have considerable significance for hormone therapy, as they reduce steroid hormone receptor expression and, thereby, the anti-proliferative action of progesterone.

Contributing Authors:
Grimm, S, NIEHS
Roberts, J, NIEHS
Chrysovergis, K, NIEHS
Bennett, B, NIEHS
Myers, P, NIEHS
Perera, L, NIEHS
Perou, C, University of North Carolina
Wade, P, NIEHS
21. Methionine Metabolism is Essential for SIRT1-regulated mESC Maintenance and Embryonic Development

Shuang Tang, NIEHS
shuang.tang2@nih.gov

Abstract:
The methionine metabolism is critical for epigenetic maintenance, redox homeostasis, and animal development. However, the regulation of methionine metabolism remains undefined. Here we provide evidence that SIRT1, the most conserved mammalian NAD+-dependent protein deacetylase, is critically involved in modulating methionine metabolism thereby impacting maintenance of mouse embryonic stem cells (mESCs) and subsequent embryogenesis. We demonstrate that SIRT1 deficient mESCs are hypersensitive to methionine restriction/depletion-induced differentiation and apoptosis, primarily due to a reduced conversion of methionine to S-adenosylmethionine. This reduction markedly decreases methylation levels of histones, resulting in dramatic alterations of gene expression profiles. Mechanistically, we show that the enzyme converting methionine to S-adenosylmethionine in mESCs, methionine adenosyltransferase 2A (MAT2A), is under control of Myc. SIRT1 modulates methionine metabolism in part through Myc-mediated expression of MAT2A. Importantly, SIRT1 KO embryos are sensitive to maternal methionine restriction-induced lethality, whereas maternal methionine supplementation increases the survival of SIRT1 KO newborn mice. Our findings uncover a novel regulatory mechanism for methionine metabolism, and highlight the importance of methionine metabolism in SIRT1-mediated mESC maintenance and embryonic development.

Contributing Authors:
Fang, Y, NIEHS
Xu, X, NIEHS
Banks, E, NIEHS
Xu, Q, NIEHS
Foley, J, NIEHS
Dowdy, S, NIEHS
Fargo, D, NIEHS
Williams, C, NIEHS
Guan, Z, Duke University
Li, X, NIEHS
22. A Novel Role for 5' to 3' Exoribonuclease Dhp1/Rat1/Xrn2: Epigenetic Silencing

James Tucker, *Wake Forest University*
jtucker@wakehealth.edu

**Abstract:**
Epigenetic gene silencing plays a critical role in regulating gene expression and contributes to organismal development and cell fate acquisition in eukaryotes. In fission yeast, *Schizosaccharomyces pombe*, heterochromatin-associated gene silencing is known to be mediated by RNA processing pathways including RNA interference (RNAi) and a 3'→5' exoribonuclease complex, the exosome. Here, we report a new RNA-processing pathway that contributes to epigenetic gene silencing and assembly of heterochromatin mediated by 5’→3’ exoribonuclease Dhp1/Rat1/Xrn2. Dhp1 mutation causes defective gene silencing both at pericentromeric regions and at the silent mating type locus. Intriguingly, mutation in either of the two well-characterized Dhp1-interacting proteins, the Din1 pyrophosphohydrolase or the Rhn1 transcription termination factor, does not result in silencing defects at the main heterochromatic regions. We demonstrate that Dhp1 interacts with heterochromatic factors and is essential in the sequential steps of establishing silencing in a manner independent of both RNAi and the exosome. Genomic and genetic analyses suggest that Dhp1 is involved in post-transcriptional silencing of repetitive regions through its RNA processing activity. The results describe the unexpected role of Dhp1/Rat1/Xrn2 in chromatin-based silencing and elucidate how various RNA-processing pathways, acting together or independently, contribute to epigenetic regulation of the eukaryotic genome.

**Contributing Authors:**
Tucker, J, *Wake Forest University*
Ohle, C, *Heidelberg University*
Schermann, G, *Heidelberg University*
Bendrin, K, *Heidelberg University*
Zhang, W, *Feinberg School of Medicine*
Fischer, T, *Heidelberg University*
Zhang, K, *Wake Forest University*
23. Uncharted Territory: a Mechanism of Reginal “Autosomal Chromosome Inactivation” in Human Development and Public Health?

Zhibin Wang, Johns Hopkins University
zwang47@jhu.edu

Abstract:
Imprinted genes are vulnerable to environmental influences during early embryonic development, thereby contributing to the onset of disease in adulthood. Numerous animal and epidemiological studies with focuses on imprinted genes have provided mechanistic insights of the developmental origin of adult disease. Recently, a large number of regular genes show random monoallelic expression (RME). Whether genes with this RME (shared allelic expression with imprinted genes) are also vulnerable to environmental factors and what epigenetic mechanism controls this RME, however, remain to be explored. Our project was originally conceived to identify unknown imprinted genes, with two approaches, referred to as NORED and MethylMosaic. The former is based on the observation that all known imprinted allele-specific-methylation patterns (ASMs) were lost in DNMT1-deficient ESCs and they were non-restorable, while the latter is based on bimodal methylation patterns of known imprinted ASMs. Bioinformatic analyses of base resolution DNA methylomes of mouse ESCs identify 2468 DNMT1-dependent regions and 2487 regions showing bimodal methylation patterns. Two approaches identified 207 regions, including known imprinted germline ASMs, that were both NORED and MethylMosaic regions. Further focused studies on candidate ASMs from two loci, Hcn2 and Park7, revealed a new paradigm that each allele actually exhibits similar propensity to be either hypo- or hypermethylated, suggesting a ‘random, switchable’ ASM. Together with published results, our data on ASMs raise a possibility of regional ‘autosomal chromosome inactivation (ACI)’-like mechanism controlling a subset of autosomal genes. We have also determined whether DNMT1-dependent or bimodal methylation patterns increase the likelihood of epigenetic perturbation from prenatal BPA and arsenic exposure. We used WGBS to compare methylomes of male fetal livers from pregnant C57BL/6 mice exposed to BPA. We found that odds ratios for CpG sites within 207 regions ranged from 4.42 to 7.73, significantly higher than control regions. The potential effect of arsenic exposure on 207 genomic regions has been actively investigated in our ongoing epigenomic profiling that was funded by TaRGET II project.

Contributing Authors:
Martos, S, Johns Hopkins University
Lou, D, Johns Hopkins University
Gao, Y, Johns Hopkins University
Bartolomei, M, University of Pennsylvania
24. Decipher and Target Cancer Cell Dependencies on Epigenetic Mutations

Greg Wang, UNC Lineberger Cancer Center
greg_wang@med.unc.edu

Abstract:
DNA methyltransferase 3A (DNMT3A) is frequently mutated in hematological cancers; however, the underlying oncogenic mechanism remains elusive. Here, we report that the DNMT3A mutational hotspot at Arg882 (DNMT3A_R882H) cooperates with NRAS mutation to transform hematopoietic stem/progenitor cells and induce acute leukemia development. Mechanistically, DNMT3A_R882H directly binds to and potentiates transactivation of stemness genes critical for leukemogenicity including Meis1, Mn1, and Hoxa gene cluster. DNMT3A_R882H induces focal epigenetic alterations, including CpG hypomethylation and concurrent gain of active histone modifications, at cis-regulatory elements such as enhancers to facilitate gene transcription. CRISPR/Cas9-mediated ablation of a putative Meis1 enhancer carrying DNMT3A_R882H-induced DNA hypomethylation impairs Meis1 expression. Importantly, DNMT3A_R882H-induced gene-expression programs can be repressed through Dot1l inhibition. Our findings not only promote mechanistic understandings of DNMT3A mutation-associated clonal and malignant hematopoiesis but also provide a therapeutic avenue for DNMT3A-mutated leukemias.


Contributing Authors:
Lu, R, University of North Carolina at Chapel Hill
Wang, P, Albert Einstein College of Medicine
Parton, T, University of North Carolina at Chapel Hill
Wade, P, NIEHS
Zheng, D, Albert Einstein College of Medicine
Wang, G, University of North Carolina at Chapel Hill
25. Gaining Insight Into Epigenetic Modifications Driving AHR-Mediated Inhibition of Osteogenesis in Human Bone-derived MSCs

AtLee Watson, North Carolina State University
atwatson@ncsu.edu

Abstract:
Bone formation requires strict coordination of transcriptional regulatory pathways to direct commitment and differentiation of mesenchymal stem cells to mature osteoblasts. There is increasing concern, however, that exposure to environmental xenobiotic stressors may perturb the osteogenic pathways responsible for normal bone formation. TCDD and other ligands to the aryl hydrocarbon receptor (AHR) are one such class of chemicals known to disrupt bone and cartilage formation in multiple in vivo models. In this study, we demonstrate AHR-mediated inhibition of osteogenesis in human bone-derived mesenchymal stem cells (hBMSCs) isolated from multiple donors through a combination of alizarin red S staining, alkaline phosphatase (ALP) activity, and RT-qPCR for select transcriptional regulators and apical markers of bone formation. Additionally, RNA-Seq was conducted on hBMSCs cultured in GM-DMSO (growth media + 0.1% DMSO, vehicle control), ODM-DMSO (osteogenic differentiation media + 0.1% DMSO) and ODM-TCDD (osteogenic differentiation media + 10 nM TCDD) at 3, 7 and 17 days post exposure. Data demonstrates differential expression of apical markers, key transcriptional regulators, and miRNA and lincRNAs known to play essential roles in osteogenic differentiation. Cells treated with both GM-DMSO and ODM-TCDD exhibit a characteristic signature of repressed osteogenic differentiation in which cells retain mesenchymal-like properties. Current efforts seek to determine key epigenetic regulators that selectively promote lineage determination though modifications within the epigenome. To date, we have identified over 300 putative epigenetic regulators (readers, writers, erasers) that are differentially expressed between GM-DMSO/ODM-DMSO, and ODM-DMSO/ODM-TCDD that may be important drivers of hBMSC fate determination.

Contributing Authors:
Dereje, J, North Carolina State University
Seth, K, North Carolina State University
26. INO80 Landscapes Chromatin Accessibility in Regulating Pluripotent State

Hongyao Yu, NIEHS
hongyao.yu@nih.gov

Abstract:
Recent studies suggest that there exist two different pluripotent states: the naive and primed state. While it is known that cells in the naive and primed state require different culture conditions, express different markers, and show different dependence on epigenetic regulators, how the two states are maintained and regulated remains largely unknown. To systematically investigate the role of INO80 in the chromatin and transcriptional regulation of the naive and primed pluripotent state in mouse ESCs and EpiSCs, we have generated an Ino80-HA mouse ESC line and carried out ChIP-seq using an anti-HA antibody in both the naive and primed pluripotent state. I found that INO80 occupies genomic regions near genes that show state-specific expression patterns, suggesting that INO80 may in cell fate maintenance. State-specific open chromatin regions were found to highly correlate with state-specific gene expression via ATAC-seq. Furthermore, INO80 occupancy is highly enriched in state-specific open chromatin regions. These results are consistent with the notion that INO80 may promote genome accessibility at state-specific genes. An Ino80 conditional knock-out (cKO) ESC line was employed to study the impact of Ino80 deletion on gene expression, nucleosome positioning, and chromatin accessibility in both the naive and primed state, to explain its differential requirement in the two states. In the primed culture condition, Ino80 deletion causes cell death and differentiation, however, to our surprise, Ino80 deletion in the 2i/LIF culture that supports the naive state shows very limited impact in both cell growth and gene expression. The above results suggest that INO80 may be selectively required for the establishment and/or maintenance of the primed state. I will carry out IP-MS for INO80 in both the naive and primed state to test the hypothesis that there may exist state-specific complex components. If successful, I will further test the function of the state-specific subunit(s). Therefore, we will comprehensively uncover the role of INO80 complex in the transition and maintenance of different pluripotent state.

Contributing Authors:
Wang, J, NIEHS
Lackford, B, NIEHS
Hu, G, NIEHS
27. Loss of fructose-1,6-bisphosphatase induces glycolysis and promotes apoptosis resistance of cancer stem-like cells: an important role in hexavalent chromium-induced carcinogenesis

Zhuo Zhang, University of Kentucky
zhuo.zhang@uky.edu

Abstract:
Hexavalent chromium (Cr(VI)) compounds are confirmed human carcinogens for lung cancer. Our previous studies have demonstrated that chronic exposure of human bronchial epithelial BEAS-2B cells to low dose of Cr(VI) causes malignant cell transformation. The acquisition of cancer stem cell-like properties is involved in the initiation of cancers. The present study has observed that a small population of cancer stem-like cells (BEAS-2B-Cr-CSC) exists in the Cr(VI)-transformed cells (BEAS-2B-Cr). Those BEAS-2B-Cr-CSC exhibit extremely reduced capability of generating reactive oxygen species (ROS) and apoptosis resistance. BEAS-2B-Cr-CSC are metabolic inactive as evidenced by reductions in oxygen consumption, glucose uptake, ATP production, and lactate production. Most importantly, BEAS-2B-Cr-CSC are more tumorigenic with high levels of cell self-renewal genes, Notch1 and p21. Further study has found that fructose-1,6-bisphosphatase (FBP1), an rate-limiting enzyme driving glyconeogenesis, was lost in BEAS-2B-Cr-CSC. Forced expression of FBP1 in BEAS-2B-Cr-CSC restored ROS generation, resulting in increased apoptosis, leading to inhibition of tumorigenesis. In summary, the present study suggests that loss of FBP1 is a critical event in tumorigenesis of Cr(VI)-transformed cells. FBP1 may function as a tumor suppressor in addition to it as a metabolic enzyme. FBP1 can be a biomarker of cancer and a target for therapeutic agents.

Contributing Authors:
Dai, J, University of Kentucky
Wang, W, University of Kentucky
Ji, Y, University of Kentucky
Kim, D, University of Kentucky
Yenwong Fai, L, University of Kentucky
Wang, L, University of Kentucky
Luo, J, University of Kentucky
Participant List
<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Email</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adelman, Karen</td>
<td>Harvard University</td>
<td><a href="mailto:karen_adelman@hms.harvard.edu">karen_adelman@hms.harvard.edu</a></td>
<td>919-402-7949</td>
</tr>
<tr>
<td>Aifantis, Iannis</td>
<td>NYU School of Medicine</td>
<td><a href="mailto:iannis.Aifantis@nyumc.org">iannis.Aifantis@nyumc.org</a></td>
<td>646-501-2965</td>
</tr>
<tr>
<td>Annab, Lois</td>
<td>NIEHS</td>
<td><a href="mailto:annab@niehs.nih.gov">annab@niehs.nih.gov</a></td>
<td>919-541-0746</td>
</tr>
<tr>
<td>Arca, Hale</td>
<td>Wake Forest Medical Center</td>
<td><a href="mailto:cigdemarca@gmail.com">cigdemarca@gmail.com</a></td>
<td>540-267-6723</td>
</tr>
<tr>
<td>Arya, Gunjan</td>
<td>North Carolina State University</td>
<td><a href="mailto:dr.gunjanyara@gmail.com">dr.gunjanyara@gmail.com</a></td>
<td>919-830-1286</td>
</tr>
<tr>
<td>Aylor, David</td>
<td>North Carolina State University</td>
<td><a href="mailto:dlaylor@ncsu.edu">dlaylor@ncsu.edu</a></td>
<td>919-515-7079</td>
</tr>
<tr>
<td>Bain, Lisa</td>
<td>Clemson University</td>
<td><a href="mailto:lbain@clemson.edu">lbain@clemson.edu</a></td>
<td>864-656-5050</td>
</tr>
<tr>
<td>Balshaw, David</td>
<td>NIEHS</td>
<td><a href="mailto:balshaw@niehs.nih.gov">balshaw@niehs.nih.gov</a></td>
<td>919-541-2448</td>
</tr>
<tr>
<td>Bardaka, Eleni</td>
<td>North Carolina State University</td>
<td><a href="mailto:ebardak@ncsu.edu">ebardak@ncsu.edu</a></td>
<td>765-412-9510</td>
</tr>
<tr>
<td>Bell, Douglas</td>
<td>NIEHS</td>
<td><a href="mailto:Bell1@niehs.nih.gov">Bell1@niehs.nih.gov</a></td>
<td>919-541-7686</td>
</tr>
<tr>
<td>Bernacki, Susan</td>
<td>North Carolina State University</td>
<td><a href="mailto:shbernac@ncsu.edu">shbernac@ncsu.edu</a></td>
<td>919-513-7710</td>
</tr>
<tr>
<td>Bridgers, Joseph</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:jbbridgers@gmail.com">jbbridgers@gmail.com</a></td>
<td>919-440-9263</td>
</tr>
<tr>
<td>Brock, Davis</td>
<td>Wake Forest University</td>
<td><a href="mailto:Brockd14@wfu.edu">Brockd14@wfu.edu</a></td>
<td>423-208-8906</td>
</tr>
<tr>
<td>Bushel, Pierre</td>
<td>NIEHS</td>
<td><a href="mailto:bushel@niehs.nih.gov">bushel@niehs.nih.gov</a></td>
<td>919-316-4564</td>
</tr>
<tr>
<td>Cao, Jingli</td>
<td>Duke University</td>
<td><a href="mailto:jingli.cao@duke.edu">jingli.cao@duke.edu</a></td>
<td>919-698-8191</td>
</tr>
<tr>
<td>Carlin, Danielle</td>
<td>NIEHS</td>
<td><a href="mailto:danielle.carlin@nih.gov">danielle.carlin@nih.gov</a></td>
<td>919-541-1409</td>
</tr>
<tr>
<td>Chan, Elizabeth</td>
<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:chan.elizabeth@epa.gov">chan.elizabeth@epa.gov</a></td>
<td>919-541-3771</td>
</tr>
<tr>
<td>Chen, Kai-Yuan</td>
<td>Duke University</td>
<td><a href="mailto:kai.yuan.chen@duke.edu">kai.yuan.chen@duke.edu</a></td>
<td>607-793-0198</td>
</tr>
<tr>
<td>Cheong, Ana</td>
<td>University of Cincinnati</td>
<td><a href="mailto:cheongaa@ucmail.uc.edu">cheongaa@ucmail.uc.edu</a></td>
<td>513-558-0595</td>
</tr>
<tr>
<td>Cho, Yoon Hee</td>
<td>University of Montana</td>
<td><a href="mailto:yoonhee.cho@umontana.edu">yoonhee.cho@umontana.edu</a></td>
<td>406-243-4529</td>
</tr>
<tr>
<td>Chorley, Brian</td>
<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:chorley.brian@epa.gov">chorley.brian@epa.gov</a></td>
<td>919-541-2329</td>
</tr>
<tr>
<td>Christy, Nicholas</td>
<td>Integrated Laboratory Systems, Inc.</td>
<td><a href="mailto:nchristy@ils-inc.com">nchristy@ils-inc.com</a></td>
<td>919-281-1110</td>
</tr>
<tr>
<td>Name</td>
<td>Affiliation</td>
<td>Email</td>
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<tr>
<td>Chrysovergis, Kali</td>
<td>NIEHS</td>
<td><a href="mailto:chrysovergik@niehs.nih.gov">chrysovergik@niehs.nih.gov</a></td>
<td>919-541-3664</td>
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<td>Cinghu, Senthilkumar</td>
<td>NIEHS</td>
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<td>Clark, Amander</td>
<td>University of California Los Angeles</td>
<td><a href="mailto:clarka@ucla.edu">clarka@ucla.edu</a></td>
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<td>Clement, Tracy</td>
<td>NIEHS</td>
<td><a href="mailto:clementbiosci@gmail.com">clementbiosci@gmail.com</a></td>
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<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:hubal.elaine@epa.gov">hubal.elaine@epa.gov</a></td>
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<td><a href="mailto:collman@niehs.nih.gov">collman@niehs.nih.gov</a></td>
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<td>Cowley, Michael</td>
<td>North Carolina State University</td>
<td><a href="mailto:macowley@ncsu.edu">macowley@ncsu.edu</a></td>
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<td>Crabtree, Gerald</td>
<td>Stanford University</td>
<td><a href="mailto:crabtree@stanford.edu">crabtree@stanford.edu</a></td>
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<td>Crona, Daniel</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:daniel.crona@unc.edu">daniel.crona@unc.edu</a></td>
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<td>Cuddapah, Suresh</td>
<td>NYU School of Medicine</td>
<td><a href="mailto:suresh.cuddapah@nyumc.org">suresh.cuddapah@nyumc.org</a></td>
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<td>Cui, Yuqi</td>
<td>Ohio State University</td>
<td><a href="mailto:cui.69@osu.edu">cui.69@osu.edu</a></td>
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<td>Curtis, Sarah</td>
<td>Emory University</td>
<td><a href="mailto:swhelan@emory.edu">swhelan@emory.edu</a></td>
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<td>U.S. Environmental Protection Agency</td>
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<td>East Carolina University</td>
<td><a href="mailto:davisnic12@students.ecu.edu">davisnic12@students.ecu.edu</a></td>
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<td>DeMayo, Francesco</td>
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<td>Deskin, Brian</td>
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<td>Dowen, Jill</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:jilldowen@unc.edu">jilldowen@unc.edu</a></td>
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<td>Drobna, Zuzana</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:zdrobna@ncsu.edu">zdrobna@ncsu.edu</a></td>
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<tr>
<td>Dronamraju, Raghuvar</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:dronamra@email.unc.edu">dronamra@email.unc.edu</a></td>
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<td>Dudek, Serena</td>
<td>NIEHS</td>
<td><a href="mailto:dudek@niehs.nih.gov">dudek@niehs.nih.gov</a></td>
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Duncan, Chris   NIEHS       duncancg@niehs.nih.gov   919-541-4476
Dunnick, June   NIEHS       dunnickj@niehs.nih.gov   919-541-4811
Enriquez, Paul   North Carolina State University    penriqu@ncsu.edu   919-999-9999
Fan, Wei   NIEHS       wei.fan2@nih.gov    919-541-0084
Fang, Yi    NIEHS       fangy4@nih.gov    919-541-0143
Fargo, David   NIEHS       fargod@niehs.nih.gov    919-541-0762
Fenton, Sue   NIEHS       fentonse@niehs.nih.gov    919-541-4141
Fleming, Jodie   North Carolina Central University    jodie.fleming@nccu.edu   919-530-6216
France, Suzanne   NIEHS contractor: MDB, Inc.    sfrance@michaeldbaker.com  919-794-4700
Frank, Jessica   U.S. Environmental Protection Agency   frank.jessica@epa.gov   919-541-4040
Gangaraju, Vamsi   Medical University of South Carolina    gangaraj@musc.edu    843-276-4918
Gao, Peisong   Johns Hopkins University     pgao1@jhmi.edu    410-550-2124
Garmire, Lana   University of Hawaii     LGarmire@hawaii.edu   808-441-8193
Ge, Kai   National Institute of Diabetes & Digestive & Kidney Diseases   kaig@niddk.nih.gov   301-451-1998
Gilliland, Frank   University of Southern California   Gillilan@usc.edu   323-442-1096
Giurgescu, Carmen   Ohio State University   giurgescu.1@osu.edu    773-218-2622
Gluck, Rob   Karyologic Inc.     robdgluck@gmail.com    919-667-8368
Gokey, Nolan   NIEHS       nolan.gokey@nih.gov    919-316-4546
Goldman, Aaron   Duke University   joseph.goldman@duke.edu   857-600-6488
Golestaneh, Nady   Georgetown University School of Medicine   ncg8@georgetown.edu    202-687-4309
Gracz, Adam   University of North Carolina at Chapel Hill   agracz@med.unc.edu   336-870-0455
Grimm, Sara   NIEHS       grimmsa@nih.gov   919-541-0086
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<td>Guo, Ge</td>
<td>University of Cambridge</td>
<td><a href="mailto:gg251@cam.ac.uk">gg251@cam.ac.uk</a></td>
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<td>Haldeman, Jonathan</td>
<td>Duke University</td>
<td><a href="mailto:jmh39@duke.edu">jmh39@duke.edu</a></td>
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<td>Halvorsen, Priya</td>
<td>NIEHS</td>
<td><a href="mailto:priya.halvorsen@nih.gov">priya.halvorsen@nih.gov</a></td>
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<td>Han, Han</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:han88@email.unc.edu">han88@email.unc.edu</a></td>
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<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:hassan.iman@epa.gov">hassan.iman@epa.gov</a></td>
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<td>Heacock, Michelle</td>
<td>NIEHS</td>
<td><a href="mailto:heacockm@niehs.nih.gov">heacockm@niehs.nih.gov</a></td>
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<td>Hewitt, Sylvia</td>
<td>NIEHS</td>
<td><a href="mailto:sylvia.hewitt@niehs.gov">sylvia.hewitt@niehs.gov</a></td>
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<td>Hilton, Isaac</td>
<td>Duke University</td>
<td><a href="mailto:isaac.hilton@duke.edu">isaac.hilton@duke.edu</a></td>
<td>573-289-3888</td>
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<td>Ho, Shuk-Mei</td>
<td>University of Cincinnati</td>
<td><a href="mailto:hosm@ucmail.uc.edu">hosm@ucmail.uc.edu</a></td>
<td>513-558-2147</td>
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<td>Hobbs, Cheryl</td>
<td>Integrated Laboratory Systems, Inc.</td>
<td><a href="mailto:chobbs@ils-inc.com">chobbs@ils-inc.com</a></td>
<td>336-343-9861</td>
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<tr>
<td>Hochedlinger, Konrad</td>
<td>Massachusetts General Hospital</td>
<td><a href="mailto:khochedlinger@helix.mgh.harvard.edu">khochedlinger@helix.mgh.harvard.edu</a></td>
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<td>Hoffman, Jackson</td>
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<td><a href="mailto:jackson.hoffman@nih.gov">jackson.hoffman@nih.gov</a></td>
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<td>Howard, Erin</td>
<td>North Carolina Central University</td>
<td><a href="mailto:ewitalis@ncsu.edu">ewitalis@ncsu.edu</a></td>
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<td><a href="mailto:guang.hu@nih.gov">guang.hu@nih.gov</a></td>
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<td>Huang, Zhiqing</td>
<td>Duke University</td>
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<td>Hudson, Katie</td>
<td>North Carolina State University</td>
<td><a href="mailto:kmbehren@ncsu.edu">kmbehren@ncsu.edu</a></td>
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<td>Il'yasova, Dora</td>
<td>Georgia State University</td>
<td><a href="mailto:dilyasova@gsu.edu">dilyasova@gsu.edu</a></td>
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<td>Jiang, Bing-Hua</td>
<td>Thomas Jefferson University</td>
<td><a href="mailto:bhjiang@jefferson.edu">bhjiang@jefferson.edu</a></td>
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<td>Jiang, Yong-hui</td>
<td>Duke University School of Medicine</td>
<td><a href="mailto:yong-hui.jiang@duke.edu">yong-hui.jiang@duke.edu</a></td>
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<td>Duke University</td>
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<td>Kalantry, Sundeep</td>
<td>University of Michigan</td>
<td><a href="mailto:kalantry@umich.edu">kalantry@umich.edu</a></td>
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<td>North Carolina State University</td>
<td><a href="mailto:ajkeung@ncsu.edu">ajkeung@ncsu.edu</a></td>
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<td>Khan, Abid</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:abid2284@email.unc.edu">abid2284@email.unc.edu</a></td>
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<td><a href="mailto:avkindev@gmail.com">avkindev@gmail.com</a></td>
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<td>Kingston, Robert</td>
<td>Massachusetts General Hospital</td>
<td><a href="mailto:Kingston@molbio.mgh.harvard.edu">Kingston@molbio.mgh.harvard.edu</a></td>
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<td>U.S. Environmental Protection Agency</td>
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<td>U.S. Environmental Protection Agency</td>
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<td>Lee, Jessica</td>
<td>North Carolina State University</td>
<td><a href="mailto:jlee64@ncsu.edu">jlee64@ncsu.edu</a></td>
<td>801-885-9031</td>
</tr>
<tr>
<td>Lee, Hyeong-Min</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:hyeong-min_lee@med.unc.edu">hyeong-min_lee@med.unc.edu</a></td>
<td>850-491-8406</td>
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<td>Lee, Chang-Lung</td>
<td>Duke University</td>
<td><a href="mailto:cl99@duke.edu">cl99@duke.edu</a></td>
<td>919-681-8683</td>
</tr>
<tr>
<td>Leung, Yuet-Kin</td>
<td>University of Cincinnati</td>
<td><a href="mailto:ricky.leung@uc.edu">ricky.leung@uc.edu</a></td>
<td>513-558-5181</td>
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<td>Name</td>
<td>Affiliation</td>
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<td>Texas A&amp;M University</td>
<td><a href="mailto:llewis@cvm.tamu.edu">llewis@cvm.tamu.edu</a></td>
<td>979-847-5692</td>
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<td>Li, Jian-Liang</td>
<td>NIEHS</td>
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<td>Li, Xiaoling</td>
<td>NIEHS</td>
<td><a href="mailto:lix3@niehs.nih.gov">lix3@niehs.nih.gov</a></td>
<td>919-541-9817</td>
</tr>
<tr>
<td>Liao, Yihan</td>
<td>Duke University</td>
<td><a href="mailto:yihan.liao@duke.edu">yihan.liao@duke.edu</a></td>
<td>608-698-4789</td>
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<td>NIEHS</td>
<td><a href="mailto:jian.liu2@nih.gov">jian.liu2@nih.gov</a></td>
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<td>Liu, Yuan</td>
<td>Florida International University</td>
<td><a href="mailto:yualiu@fiu.edu">yualiu@fiu.edu</a></td>
<td>919-308-1616</td>
</tr>
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<td>Liu, Fang</td>
<td>Duke University</td>
<td><a href="mailto:fangliu@neuro.duke.edu">fangliu@neuro.duke.edu</a></td>
<td>919-681-1993</td>
</tr>
<tr>
<td>Livanos Gonzalez, Elizabeth</td>
<td>KaryoLogic, Inc.</td>
<td><a href="mailto:info@karyologic.com">info@karyologic.com</a></td>
<td>919-632-6111</td>
</tr>
<tr>
<td>Lozoya, Oswaldo</td>
<td>NIEHS</td>
<td><a href="mailto:oswaldo.lozoya@nih.gov">oswaldo.lozoya@nih.gov</a></td>
<td>919-541-0744</td>
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<td>Lu, Rui</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:ruilu@med.unc.edu">ruilu@med.unc.edu</a></td>
<td>919-966-5953</td>
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<td>Lunn, Ruth</td>
<td>NIEHS</td>
<td><a href="mailto:lunn@niehs.nih.gov">lunn@niehs.nih.gov</a></td>
<td>919-316-4637</td>
</tr>
<tr>
<td>Luz, Anthony</td>
<td>NIEHS</td>
<td><a href="mailto:tluz88@yahoo.com">tluz88@yahoo.com</a></td>
<td>518-231-2611</td>
</tr>
<tr>
<td>Mabe, Nathaniel</td>
<td>Duke University</td>
<td><a href="mailto:nwm9@duke.edu">nwm9@duke.edu</a></td>
<td>740-248-2295</td>
</tr>
<tr>
<td>Mackey, Lantz</td>
<td>NIEHS</td>
<td><a href="mailto:lantz.mackey@nih.gov">lantz.mackey@nih.gov</a></td>
<td>540-729-6040</td>
</tr>
<tr>
<td>Marcel, Shelsa</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:shelsa@email.unc.edu">shelsa@email.unc.edu</a></td>
<td>340-227-3977</td>
</tr>
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<td>Marcus, Michele</td>
<td>Emory University</td>
<td><a href="mailto:mmarcus@emory.edu">mmarcus@emory.edu</a></td>
<td>404-727-8010</td>
</tr>
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<td>Martin, Negin</td>
<td>NIEHS</td>
<td><a href="mailto:martin12@niehs.nih.gov">martin12@niehs.nih.gov</a></td>
<td>919-541-7751</td>
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<td>McAllister, Kim</td>
<td>NIEHS</td>
<td><a href="mailto:mcallis2@niehs.nih.gov">mcallis2@niehs.nih.gov</a></td>
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<td><a href="mailto:mccullough.shaun@epa.gov">mccullough.shaun@epa.gov</a></td>
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<td>McNabb, Nicole</td>
<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:mcnabb.nicole@epa.gov">mcnabb.nicole@epa.gov</a></td>
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<tr>
<td>Meanor, Jenna</td>
<td>North Carolina State University</td>
<td><a href="mailto:jnmeanor@ncsu.edu">jnmeanor@ncsu.edu</a></td>
<td>919-608-0768</td>
</tr>
<tr>
<td>Meriesh, Hashem</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:hashem@unc.edu">hashem@unc.edu</a></td>
<td>571-435-6228</td>
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<tr>
<td>Name</td>
<td>Institution</td>
<td>Email</td>
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<td>Meyer, Kate</td>
<td>Duke University</td>
<td><a href="mailto:kate.meyer@duke.edu">kate.meyer@duke.edu</a></td>
<td>919-684-9562</td>
</tr>
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<td>Meyer, Joel</td>
<td>Duke University</td>
<td><a href="mailto:joel.meyer@duke.edu">joel.meyer@duke.edu</a></td>
<td>919-806-7968</td>
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<tr>
<td>Miranda, Adam</td>
<td>North Carolina State University</td>
<td><a href="mailto:axmirand@ncsu.edu">axmirand@ncsu.edu</a></td>
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<tr>
<td>Mudipalli, Anuradha</td>
<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:mudipalli.anu@epa.gov">mudipalli.anu@epa.gov</a></td>
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<td>Murashov, Alexander</td>
<td>East Carolina University</td>
<td><a href="mailto:murashoval@ecu.edu">murashoval@ecu.edu</a></td>
<td>252-341-0648</td>
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<tr>
<td>Murthy, Preetish</td>
<td>Duke University</td>
<td><a href="mailto:pk434@cornell.edu">pk434@cornell.edu</a></td>
<td>607-379-9485</td>
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<tr>
<td>Nag, Mukta</td>
<td>North Carolina State University</td>
<td><a href="mailto:mnag@ncsu.edu">mnag@ncsu.edu</a></td>
<td>919-720-3955</td>
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<td>Narayan, Roger</td>
<td>North Carolina State University</td>
<td><a href="mailto:rjnaraya@ncsu.edu">rjnaraya@ncsu.edu</a></td>
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<tr>
<td>Nguyen, Thuy-Ai</td>
<td>NIEHS</td>
<td><a href="mailto:thuy-ai.nguyen@nih.gov">thuy-ai.nguyen@nih.gov</a></td>
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<td>Nichols, Harriette</td>
<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:nichols.harriette@epa.gov">nichols.harriette@epa.gov</a></td>
<td>919-541-2335</td>
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<tr>
<td>Pal, Anandita</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:dita991@email.unc.edu">dita991@email.unc.edu</a></td>
<td>980-234-0015</td>
</tr>
<tr>
<td>Pan, William</td>
<td>Duke University</td>
<td><a href="mailto:wkp@duke.edu">wkp@duke.edu</a></td>
<td>919-684-4108</td>
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<tr>
<td>Papadeas, Sophia</td>
<td>Elaion LLC</td>
<td><a href="mailto:spapade1@yahoo.com">spapade1@yahoo.com</a></td>
<td>443-739-9596</td>
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<td>Park, Yong-Moon</td>
<td>NIEHS</td>
<td><a href="mailto:mark.park@nih.gov">mark.park@nih.gov</a></td>
<td>919-541-3630</td>
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<td>Parris, Amanda</td>
<td>North Carolina Central University</td>
<td><a href="mailto:ablack18@nccu.edu">ablack18@nccu.edu</a></td>
<td>704-706-5445</td>
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<tr>
<td>Pathania, Rajneesh</td>
<td>NIEHS</td>
<td><a href="mailto:rajneesh.pathania@nih.gov">rajneesh.pathania@nih.gov</a></td>
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<td>Phillips, Bart</td>
<td>NIEHS</td>
<td><a href="mailto:bart.phillips@nih.gov">bart.phillips@nih.gov</a></td>
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<tr>
<td>Poston, Robert</td>
<td>University of California, Merced</td>
<td><a href="mailto:rposton@ucmerced.edu">rposton@ucmerced.edu</a></td>
<td>317-645-7163</td>
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<tr>
<td>Puga, Alvaro</td>
<td>University of Cincinnati</td>
<td><a href="mailto:Alvaro.Puga@uc.edu">Alvaro.Puga@uc.edu</a></td>
<td>513-558-0916</td>
</tr>
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<td>NIEHS</td>
<td><a href="mailto:qiny@niehs.nih.gov">qiny@niehs.nih.gov</a></td>
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<td>Randall, Thomas</td>
<td>NIEHS</td>
<td><a href="mailto:randallta2@niehs.nih.gov">randallta2@niehs.nih.gov</a></td>
<td>919-541-2271</td>
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<tr>
<td>Rao, Anjana</td>
<td>La Jolla Institute for Allergy and Immunology</td>
<td><a href="mailto:arao@lji.org">arao@lji.org</a></td>
<td>858-952-7161</td>
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<td>Name</td>
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<td>North Carolina State University</td>
<td><a href="mailto:bmrao@ncsu.edu">bmrao@ncsu.edu</a></td>
<td>919-513-0129</td>
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<tr>
<td>Ravindranath, Ravi</td>
<td>National Institute of Child Health and Human Development</td>
<td><a href="mailto:ravindrn@mail.nih.gov">ravindrn@mail.nih.gov</a></td>
<td>301-435-6889</td>
</tr>
<tr>
<td>Recio, Leslie</td>
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<td><a href="mailto:ilrecio@ils-inc.com">ilrecio@ils-inc.com</a></td>
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<tr>
<td>Reinlib, Les</td>
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<td><a href="mailto:reinlib@niehs.nih.gov">reinlib@niehs.nih.gov</a></td>
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</tr>
<tr>
<td>Ren, Xuefeng</td>
<td>University at Buffalo</td>
<td><a href="mailto:xuefengr@buffalo.edu">xuefengr@buffalo.edu</a></td>
<td>716-829-5384</td>
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<tr>
<td>Roberts, John</td>
<td>NIEHS</td>
<td><a href="mailto:roberts1@niehs.nih.gov">roberts1@niehs.nih.gov</a></td>
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<tr>
<td>Rogers, John</td>
<td>U.S. Environmental Protection Agency</td>
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<tr>
<td>Ruden, Douglas</td>
<td>Wayne State University</td>
<td><a href="mailto:douglasr@wayne.edu">douglasr@wayne.edu</a></td>
<td>313-577-6688</td>
</tr>
<tr>
<td>Saha, Ramendra</td>
<td>University of California, Merced</td>
<td><a href="mailto:rsaha3@ncmerced.edu">rsaha3@ncmerced.edu</a></td>
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<tr>
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<td>NIEHS</td>
<td><a href="mailto:janine.santos@nih.gov">janine.santos@nih.gov</a></td>
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<tr>
<td>Seidler, Fred</td>
<td>Duke University Medical Center</td>
<td><a href="mailto:seidler@duke.edu">seidler@duke.edu</a></td>
<td>919-684-2315</td>
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<tr>
<td>Shats, Igor</td>
<td>NIEHS</td>
<td><a href="mailto:shatsi2@nih.gov">shatsi2@nih.gov</a></td>
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<td>Shatz, Maria</td>
<td>NIEHS</td>
<td><a href="mailto:shatzm@niehs.nih.gov">shatzm@niehs.nih.gov</a></td>
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<tr>
<td>Shaughnessy, Dan</td>
<td>NIEHS</td>
<td><a href="mailto:Shaughn1@niehs.nih.gov">Shaughn1@niehs.nih.gov</a></td>
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<tr>
<td>Shaw, Natalie</td>
<td>NIEHS</td>
<td><a href="mailto:natalie.shaw@nih.gov">natalie.shaw@nih.gov</a></td>
<td>919-564-5458</td>
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<tr>
<td>Shehee, Mina</td>
<td>North Carolina Department of Health and Human Services</td>
<td><a href="mailto:mina.shehee@dhhs.nc.gov">mina.shehee@dhhs.nc.gov</a></td>
<td>919-707-5920</td>
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<tr>
<td>Sherr, David</td>
<td>Boston University</td>
<td><a href="mailto:dsherr@bu.edu">dsherr@bu.edu</a></td>
<td>617-638-6464</td>
</tr>
<tr>
<td>Shi, Xianglin</td>
<td>University of Kentucky</td>
<td><a href="mailto:xianglin.shi@uky.edu">xianglin.shi@uky.edu</a></td>
<td>859-257-4054</td>
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<tr>
<td>Shi, Yuming</td>
<td>Duke University</td>
<td><a href="mailto:ys139@duke.edu">ys139@duke.edu</a></td>
<td>919-454-8706</td>
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<tr>
<td>Shiekhattar, Ramin</td>
<td>University of Miami</td>
<td><a href="mailto:rshiekhattar@med.miami.edu">rshiekhattar@med.miami.edu</a></td>
<td>305-243-4579</td>
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<tr>
<td>Shilatifard, Ali</td>
<td>Northwestern University</td>
<td><a href="mailto:ash@northwestern.edu">ash@northwestern.edu</a></td>
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<tr>
<td>Singh, Ajeet</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:singhap@email.unc.edu">singhap@email.unc.edu</a></td>
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<td>Integrated Laboratory Systems, Inc.</td>
<td><a href="mailto:nishi.sinha@gmail.com">nishi.sinha@gmail.com</a></td>
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<tr>
<td>Sivanandane, Sittadjody</td>
<td>Wake Forest Institute for Regenerative Medicine</td>
<td><a href="mailto:ssivanan@wakehealth.edu">ssivanan@wakehealth.edu</a></td>
<td>336-926-2938</td>
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<td>Smith, Hannah</td>
<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:hannahjo@live.unc.edu">hannahjo@live.unc.edu</a></td>
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<td>Stein, Paula</td>
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<td><a href="mailto:paula.stein@nih.gov">paula.stein@nih.gov</a></td>
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<td>NIEHS</td>
<td><a href="mailto:alisa.suen@gmail.com">alisa.suen@gmail.com</a></td>
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<td>Tam, Ryan</td>
<td>North Carolina State University</td>
<td><a href="mailto:rwtam@ncsu.edu">rwtam@ncsu.edu</a></td>
<td>408-933-8286</td>
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<td>Tam, Neville</td>
<td>University of Cincinnati</td>
<td><a href="mailto:neville.tam@uc.edu">neville.tam@uc.edu</a></td>
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<td>Tang, Shuang</td>
<td>NIEHS</td>
<td><a href="mailto:shuang.tang2@nih.gov">shuang.tang2@nih.gov</a></td>
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<tr>
<td>Tarapore, Pheruza</td>
<td>University of Cincinnati</td>
<td><a href="mailto:pheruza.tarapore@uc.edu">pheruza.tarapore@uc.edu</a></td>
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<tr>
<td>Taylor, Hugh</td>
<td>Yale University</td>
<td><a href="mailto:hugh.taylor@yale.edu">hugh.taylor@yale.edu</a></td>
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<td>U.S. Environmental Protection Agency</td>
<td><a href="mailto:thai.sheau-fung@epa.gov">thai.sheau-fung@epa.gov</a></td>
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<tr>
<td>Tlsty, Thea</td>
<td>University of California San Francisco</td>
<td><a href="mailto:thea.tlstry@ucsf.edu">thea.tlstry@ucsf.edu</a></td>
<td>415-566-5450</td>
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<td>Tomek, Kyle</td>
<td>North Carolina State University</td>
<td><a href="mailto:kjtomek@ncsu.edu">kjtomek@ncsu.edu</a></td>
<td>810-449-6778</td>
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<td>Trempus, Carol</td>
<td>NIEHS</td>
<td><a href="mailto:trempus@niehs.nih.gov">trempus@niehs.nih.gov</a></td>
<td>919-541-0240</td>
</tr>
<tr>
<td>Tretjakova, Natalia</td>
<td>University of Minnesota</td>
<td><a href="mailto:trety001@umn.edu">trety001@umn.edu</a></td>
<td>612-626-3432</td>
</tr>
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<td>NIEHS</td>
<td><a href="mailto:trotter@niehs.nih.gov">trotter@niehs.nih.gov</a></td>
<td>919-316-4654</td>
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<tr>
<td>Tucker, James</td>
<td>Wake Forest University</td>
<td><a href="mailto:jtucker@wakehealth.edu">jtucker@wakehealth.edu</a></td>
<td>864-918-0083</td>
</tr>
<tr>
<td>Tung, Kuei-Ling</td>
<td>Duke University</td>
<td><a href="mailto:kt173@duke.edu">kt173@duke.edu</a></td>
<td>607-279-3380</td>
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<td>Turlapati, Lavanya</td>
<td>North Carolina State University</td>
<td><a href="mailto:lturlap@ncsu.edu">lturlap@ncsu.edu</a></td>
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<td>Twist, Joanna</td>
<td>NIEHS</td>
<td><a href="mailto:joanna.twist@nih.gov">joanna.twist@nih.gov</a></td>
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<td>NIEHS</td>
<td><a href="mailto:tyson2@niehs.nih.gov">tyson2@niehs.nih.gov</a></td>
<td>919-541-0176</td>
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<tr>
<td>Vitucci, Eva</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:evav1@email.unc.edu">evav1@email.unc.edu</a></td>
<td>321-693-1372</td>
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<tr>
<td>Voelker, Kerri</td>
<td>NIEHS Contractor: MDB, Inc.</td>
<td><a href="mailto:kvoelker@michaeldbaker.com">kvoelker@michaeldbaker.com</a></td>
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<td>Wade, Paul</td>
<td>NIEHS</td>
<td><a href="mailto:wadep2@niehs.nih.gov">wadep2@niehs.nih.gov</a></td>
<td>919-541-3392</td>
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<tr>
<td>Wang, Zhibin</td>
<td>Johns Hopkins University</td>
<td><a href="mailto:zwang47@jhu.edu">zwang47@jhu.edu</a></td>
<td>410-955-7840</td>
</tr>
<tr>
<td>Wang, Greg</td>
<td>UNC Lineberger Cancer Center</td>
<td><a href="mailto:greg_wang@med.unc.edu">greg_wang@med.unc.edu</a></td>
<td>919-966-5953</td>
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<td>Watson, AtLee</td>
<td>North Carolina State University</td>
<td><a href="mailto:atwatson@ncsu.edu">atwatson@ncsu.edu</a></td>
<td>919-603-4653</td>
</tr>
<tr>
<td>Weinhouse, Caren</td>
<td>Duke University</td>
<td><a href="mailto:caren.weinhouse@duke.edu">caren.weinhouse@duke.edu</a></td>
<td>248-508-0047</td>
</tr>
<tr>
<td>Wicha, Max</td>
<td>University of Michigan Cancer Center</td>
<td><a href="mailto:mwicha@med.umich.edu">mwicha@med.umich.edu</a></td>
<td>734-763-1744</td>
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<td>Williams, Carmen</td>
<td>NIEHS</td>
<td><a href="mailto:williamscc5@niehs.nih.gov">williamscc5@niehs.nih.gov</a></td>
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<td>Wu, Steve</td>
<td>NIEHS</td>
<td><a href="mailto:steve.wu@nih.gov">steve.wu@nih.gov</a></td>
<td>919-316-4042</td>
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<td>Xu, Hong</td>
<td>NIEHS</td>
<td><a href="mailto:hxu.hong@gmail.com">hxu.hong@gmail.com</a></td>
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<td>Xu, Miaofei</td>
<td>NIEHS</td>
<td><a href="mailto:miaofei.xu@nih.gov">miaofei.xu@nih.gov</a></td>
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<td><a href="mailto:xuxiao@niehs.nih.gov">xuxiao@niehs.nih.gov</a></td>
<td>919-541-7762</td>
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<td>Yang, Xiaoh</td>
<td>North Carolina Central University</td>
<td><a href="mailto:xyang@nccu.edu">xyang@nccu.edu</a></td>
<td>704-250-5726</td>
</tr>
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<td>Yang, Tianqi</td>
<td>Duke University</td>
<td><a href="mailto:ty48@duke.edu">ty48@duke.edu</a></td>
<td>919-684-0636</td>
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<tr>
<td>Yeo, Michelle</td>
<td>Duke University</td>
<td><a href="mailto:myeo@duke.edu">myeo@duke.edu</a></td>
<td>919-684-4826</td>
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<tr>
<td>Yildirim, Eda</td>
<td>Duke University School of Medicine</td>
<td><a href="mailto:eda.yildirim@duke.edu">eda.yildirim@duke.edu</a></td>
<td>617-756-3139</td>
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<td>Zeldin, Darryl</td>
<td>NIEHS</td>
<td><a href="mailto:zeldin@niehs.nih.gov">zeldin@niehs.nih.gov</a></td>
<td>919-541-1169</td>
</tr>
<tr>
<td>Zhang, Yanqiong</td>
<td>University of North Carolina at Chapel Hill</td>
<td><a href="mailto:yanqiong_zhang@med.unc.edu">yanqiong_zhang@med.unc.edu</a></td>
<td>252-412-3571</td>
</tr>
<tr>
<td>Zhang, Ke</td>
<td>Wake Forest University</td>
<td><a href="mailto:zhangk@wfu.edu">zhangk@wfu.edu</a></td>
<td>336-758-2018</td>
</tr>
<tr>
<td>Zhang, Zhuo</td>
<td>University of Kentucky</td>
<td><a href="mailto:zhuo.zhang@uky.edu">zhuo.zhang@uky.edu</a></td>
<td>859-323-9591</td>
</tr>
<tr>
<td>Name</td>
<td>Affiliation</td>
<td>Email</td>
<td>Phone</td>
</tr>
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</tr>
<tr>
<td>Zhang, Shaoping</td>
<td>University of North Carolina at Chapel Hill School of Dentistry</td>
<td><a href="mailto:shaoping_zhang@unc.edu">shaoping_zhang@unc.edu</a></td>
<td>919-537-3417</td>
</tr>
<tr>
<td>Zhao, Fei</td>
<td>NIEHS</td>
<td><a href="mailto:fei.zhao2@nih.gov">fei.zhao2@nih.gov</a></td>
<td>919-519-8062</td>
</tr>
<tr>
<td>Zwaka, Thomas</td>
<td>Icahn School of Medicine at Mount Sinai</td>
<td><a href="mailto:thomas.zwaka@mssm.edu">thomas.zwaka@mssm.edu</a></td>
<td>212-659-8293</td>
</tr>
</tbody>
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