

PENN EPIGENETICS INSTITUTE

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**MARISA
BARTOLOMEI, PH.D.**

*Professor of Cell and
Developmental Biology
Co-Director, Epigenetics
Institute*

Faculty Website

<http://cdb.med.upenn.edu/people/marisa-s-bartolomei-ph-d>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9-123 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-898-9063
Lab: 215 898-9277
bartolom@pennmedicine.upenn.edu

Research Interest

The research in the Bartolomei laboratory focuses epigenetic control of genomic imprinting. They also study how the environment can perturb genomic imprinting and other epigenetic processes important in reproduction and health.



**SHELLEY L.
BERGER, PH.D.**

*Daniel S. Och University
Professor; Director,
Epigenetics Institute
Penn Integrated Knowledge
Professor (PIK)*

Lab Website

<http://hosting.med.upenn.edu/epigenetics/berger>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g275/p863>
<https://pikprofessors.upenn.edu>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology; Biology; Genetics
9-125 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-746-3106
Lab: 215-746-8223
bergers@pennmedicine.upenn.edu

Research Interest

Our laboratory studies epigenetic regulation in a variety of model systems (*S. cerevisiae*, mouse, human cells, and eusocial insects), focusing on chromatin mechanisms underlying aging, gametogenesis, cancer (p53 regulation), and animal behavior



**GERD
BLOBEL, M.D., PH.D.**

*Frank E. Weise III Professor
of Pediatrics; Co-Director,
Epigenetics Institute*

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20000343/p1105>

Contact Information

The Children's Hospital of Philadelphia
Perelman School of Medicine
University of Pennsylvania
3615 Civic Center Blvd. ARC 316H
Philadelphia, PA 19104
Phone: (215) 590-3988
Fax: (215) 590-4834
blobel@email.chop.edu

Research Interest

We study how tissue-specific transcription factors govern the specification and maintenance of hematopoietic cell lineages. We examine how transcription programs are epigenetically transmitted through mitosis to maintain lineage identity, and how genetic regulatory elements are organized spatially within the nucleus.



CORE FACULTY



**MONSERRAT
ANGUERA, PH.D.**

*Assistant Professor,
Department of Biomedical
Sciences, University of
Pennsylvania School of
Veterinary Medicine*

Lab Website

<http://www.vet.upenn.edu/research/research-laboratories/research-laboratory/anguera-laboratory>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20001040/p8634094>

Contact Information

University of Pennsylvania
School of Veterinary Medicine
3800 Spruce St., Rm 390EB
Philadelphia, PA 19104
Tel: 215.898.0567
Cell: 617.959.9993
FAX: 215.573.6810
Email: anguera@vet.upenn.edu

Research Interest

The research in the Anguera laboratory focuses on maintenance of X-chromosome inactivation in the immune system and in stem cells. They also study epigenetic mechanisms involving long noncoding RNAs during early human development and placental progenitors.



**IRFAN A.
ASANGANI, PH.D.**

*Assistant Professor of
Cancer Biology; Assistant
Investigator, Abramson
Family Cancer Research
Institute*

Faculty Website

<http://www.cbio.med.upenn.edu/bioTemplate.asp?pagelD=7>

Contact Information

Perelman School of Medicine at the University of Pennsylvania
Department of Cancer Biology
Abrasion Family Cancer Research Institute
421 Curie Boulevard
611 BRB II/III
Philadelphia, PA 19104-6160
Office: (215)746-8780
Fax: (215)573-6725
asangani@pennmedicine.upenn.edu

Research Interest

Cancer cells display an altered landscape of chromatin leading to broad changes in the gene expression. In addition, genes involved in chromatin remodeling and epigenetic regulation are frequently and specifically mutated in a wide variety of cancers including prostate cancer. While known to serve important roles in the control of gene expression and development, these largely unexpected mutation findings have illuminated newly recognized mechanisms central to the genesis of cancer. Gaining insight into the mechanism of chromatin regulation in cancer will offer the potential to reveal novel approaches and targets for effective therapeutic intervention.

Our laboratory employs a multidisciplinary approach to study these molecular epigenetic events associated with cancer towards the overarching goal of translating this knowledge into clinical tools by developing novel diagnostic, prognostic and therapeutic strategies. Additionally, we investigate the mechanisms of resistance to targeted therapies and develop novel combinatorial approaches that act on compensatory/new pathways in resistant tumors. Our basic strategy is to develop and deploy rational polytherapy upfront that suppresses the survival and emergence of resistant tumor cells.



BEN E. BLACK, PH.D.

*Associate Professor of
Biochemistry and Biophysics*

Lab Website

<http://hosting.med.upenn.edu/blacklab>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20x000321/p812847>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Biochemistry and Biophysics
422 Curie Blvd.
913A Stellar-Chance
Philadelphia, PA 19104-6059
Office: (215) 898-5039
Fax: (215) 573-7058
blackbe@pennmedicine.upenn.edu

Research Interest

The Black Lab is interested in how particular proteins direct accurate chromosome segregation at mitosis. The work in the lab involves building

centromeric chromatin that directs chromosome inheritance from its component parts for analysis of its physical characteristics, developing biochemical assays to reconstitute steps in the process of establishing and maintaining the epigenetic mark, exploiting emerging genomic and epigenomic technologies to investigate the structure of centromeric chromatin, and using cell-based approaches to study the behavior of proteins involved in centromere inheritance and other essential aspects related to chromosome segregation at cell division.



**ROBERTO
BONASIO, PH.D.**

*Assistant Professor of Cell
and Developmental Biology*

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/p8678096>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9-111 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-573-2598
rbon@pennmedicine.upenn.edu

Research Interest

The Bonasio laboratory investigates the molecular mechanisms of epigenetic memory with a focus on the role of noncoding RNAs. These processes are key to a number of biological phenomena, including embryonic development, cancer, stem cell pluripotency, and brain function. We approach these fundamental biological questions from both a mechanistic and systems-level perspective. We combine biochemistry and molecular biology with bioinformatics and genomics in conventional systems, such as mammalian cells, and nonconventional model organisms, such as ants, which offer new, unexplored avenues to study epigenetics.



**BRIAN C.
CAPELL, M.D., PH.D.**

*Assistant Professor of
Dermatology*

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20001040/p8634094>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
421 Curie Boulevard
1020-21 BRB II/III
Philadelphia, PA 19104
Office: 215-662-2737
brian.capell@uphs.upenn.edu

Research Interest

Epithelial tissues rely on a highly coordinated balance between self-renewal, proliferation, and differentiation. Epigenetic mechanisms provide this precise control through the regulation of gene enhancer and transcriptional networks that establish and maintain cell fate and identity. Disruption of these pathways can lead to a loss of proliferative control, ultimately driving cancer.

Consistent with this, chromatin regulators are amongst the most frequently mutated genes in all of cancer, with an exceptionally high incidence of mutations in cancers of self-renewing epithelial tissues, such as squamous cell carcinoma (SCC). SCC is the

most common type of cancer worldwide, affecting numerous epithelial tissues ranging from the skin and eyes to the lung, esophagus, and oropharynx. Despite this, precisely how disruption of epigenetic homeostasis may drive epithelial cancers such as SCC is poorly understood.

In the Capell Lab, we combine cutting-edge epigenetic technologies, human patient samples, primary cells, and mouse models in order to solve several fundamental unanswered questions:

- * How is the skin epigenome altered by intrinsic (i.e. aging) and extrinsic (i.e. ultraviolet radiation) environmental influences, and how do these changes contribute to disease?
- * How do chromatin regulatory enzymes function in both normal and diseased skin, particularly during carcinogenesis?
- * Can we target the epigenome with precision to treat disease?

Through this, we hope to identify new epigenetic targets for prevention and treatment of these potentially deadly cancers.



**MAYA
CAPELSON, PH.D.**

*Assistant Professor of Cell
and Developmental Biology*

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g275/p8634094>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9-101 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-898-0550
Lab: 215-573-7548
capelson@pennmedicine.upenn.edu

Research Interest

The Capelson lab is interested in how the genome is organized inside the nucleus and how this organization contributes to functional regulation of gene activity. Our recent work demonstrated that components of the Nuclear Pore Complex bind and functionally regulate genes undergoing developmental activation. Our current model envisions Nuclear Pores as active participants in the establishment and maintenance of chromatin organization through physical interactions with specific regions of the genome. Using our approaches of *Drosophila* genetics, chromatin mapping, and high-resolution microscopy, we aim to understand how these interactions are mediated, how they can change in development or disease states, and how they influence the establishment and inheritance of gene expression patterns.



**JONATHAN A.
EPSTEIN, M.D.**

*Executive Vice Dean and
Chief Scientific Officer
William Wikoff Smith
Professor of Medicine*

Lab Website

<https://www.pennmedicine.org/departments-and-centers/penn-cardiovascular-institute/members/principal-investigators/epstein-lab>

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g275/p12834>

Contact Information

University of Pennsylvania
Perelman School of Medicine
602 PCAM South Expansion
3400 Civic Center Blvd.
Philadelphia, PA 19104
Office: 215-898-8731
Fax: 215-573-2030
epsteinj@pennmedicine.upenn.edu

Research Interest

The Epstein laboratory studies molecular mechanisms of cardiovascular development and stem cell biology, and the implications of these mechanisms for understanding human disease. The lab has a longstanding interest in the genetic causes of congenital heart disease and transcriptional regulation of cell fate determination. Most recently, we have focused on epigenetics, including the role of histone deacetylases in cardiac development and adult heart function. Aims of current projects include gaining an understanding of the three-dimensional packaging of DNA and chromatin in the nucleus ("nuclear architecture"), and the regulation of cell differentiation by protein complexes that tether regions of the genome to the nuclear periphery. The lab has pioneered the concept that interactions between the nuclear lamina and the chromatin contribute to the regulation of entire gene programs that define cardiac cell types.



**BENJAMIN
GARCIA, PH.D.**

*Presidential Professor of
Biochemistry and Biophysics
Director of Quantitative
Proteomics*

Lab Website

<http://hosting.med.upenn.edu/garcialab>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g275/p8555910>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Epigenetics Program
Department of Biochemistry and Biophysics
Smilow Center for Translational Research
Room 9-124 (office)
Room 9-175C (Lab)
3400 Civic Center Blvd, Bldg 421
Philadelphia, PA 19104-5157
Office: 215-573-9423
Lab: 215-573-9422
bgarci@pennmedicine.upenn.edu

Research Interest

The Garcia lab is interested in the development and application of quantitative mass spectrometry based proteomics for understanding dynamic proteome and protein post-translational modifications. In particular, we are interested in understanding combinatorial histone PTMs and their role in regulating gene expression.



**ROGER
GREENBERG M.D., PH.D.**

*Professor, Department of
Cancer Biology; Director of
Basic Science, Bassett Center
for BRCA; Investigator,
Abramson Family Cancer
Research Institute*

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20001500/p8145566>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cancer Biology
Abramson Family Cancer Research Institute
421 Curie Boulevard
513 BRB II/III
Philadelphia, PA 19104-6160
Office: 215-746-2738
Fax: 215-573-2486
Lab: 215-746-7799
rogergr@pennmedicine.upenn.edu

Research Interest

The Greenberg lab is interested in understanding how chromatin responses to DNA damage impact genome integrity, cancer susceptibility, and response to anti-cancer therapy. Our basic findings have led to the identification of three new breast cancer susceptibility genes, a human syndrome associated with biallelic BRCA1 mutations, and insights into mechanisms by which chromatin responses affect response to targeted therapies.



**ELIZABETH
HELLER, PH.D.**

*Assistant Professor of
Pharmacology*

Lab Website

<http://www.med.upenn.edu/hellerlab>

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/p6386743>

Contact Information

Laboratory of Neuroepigenetics
Department of Systems Pharmacology and
Translational Therapeutics
Institute for Translational Medicine and Therapeutics
10-115 Smilow Center for Translational Research
3400 Civic Center Boulevard, Building 421
Philadelphia, PA 19104
Office: 215 573-7038
eheller@pennmedicine.upenn.edu

Research Interest

The Heller Lab studies the mechanisms by which remodeling of the epigenome leads to aberrant neuronal gene function and behavior. To approach this problem, we directly manipulate histone and DNA modifications at specific genes in vivo, using viral delivery of epigenetic editing tools. We focus on uncovering the mechanisms by which chromatin modifications interact with the transcriptional machinery following exposure to psychostimulants, such as drugs of abuse and stress. Because the behavioral disease traits of addiction and depression persist long after cessation of the harmful experience, stable epigenetic remodeling is an attractive mechanism for such long-lasting effects and presents an intriguing target for therapeutic intervention.



ERIC F. JOYCE, PH.D.

*Assistant Professor
of Genetics*

Lab Website

<https://ericjoycelab.com>

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g275/p8867860>

Contact Information

564 Clinical Research Building
415 Curie Boulevard
Philadelphia, PA 19104-6145
Office: 215-898-1229
Lab: 215-746-5734
erjoyce@pennmedicine.upenn.edu

Research Interest

Our laboratory studies the spatial organization of the genome, with implications for gene regulation, genome integrity, and diseases such as cancer, aging, and neurodegenerative disorders. We use *Drosophila* and mammalian systems in combination with cellular, molecular, genetic, and computational tools to elucidate how the structure and position of chromosomes within the nucleus is established and inherited across cell divisions.



**KLAUS
KAESTNER, PH.D., M.S.**

*Thomas and Evelyn Suor
Butterworth Professor in
Genetics; Director, Center of
Excellence in Type 1 Diabetes
Associate Director, Penn
Diabetes Research Center
Associate Director, Penn
Center for Molecular Studies in
Digestive and Liver Diseases;
Director, Next Generation
Sequencing Center*

Lab Website

<http://www.med.upenn.edu/kaestnerlab>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g275/p389>

Contact Information

12-126 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6145
Phone: 215-898-8759
Fax: 215-573-5892
kaestner@pennmedicine.upenn.edu

Research Interest

The Kaestner lab employs modern mouse genetic approaches, such as gene targeting, tissue-specific and inducible gene ablation, to understand the molecular mechanisms of organogenesis and physiology of the liver, pancreas and gastrointestinal tract. We also employ next-generation sequencing to explore the differences between the transcriptome and epigenome of normal vs diseased tissues.

The prevalence of Diabetes Mellitus has reached epidemic proportions world-wide, and is predicted to increase rapidly in the years to come, putting a tremendous strain on health care budgets in both developed and developing countries. There are two major forms of diabetes and both are associated with decreased beta-cell mass. No treatments have been devised that increase beta-cell mass in vivo in humans, and transplantation of beta-cells is extremely limited due to lack of appropriate donors. For these reasons, increasing functional beta-cell mass in vitro, or in vivo prior to or after transplantation, has become a "Holy Grail" of diabetes research. Our previous studies clearly show that adult human beta-cells can be induced to replicate, and – importantly – that cells can maintain normal glucose responsiveness after cell division. However, the replication rate achieved was still low, likely due in part to the known

age-related decline in the ability of the beta-cell to replicate. We propose to build on our previous findings and to develop more efficacious methods to increase functional beta-cell mass by inducing replication of adult beta-cells, and by restoring juvenile functional properties to aged beta-cells. We will focus on mechanisms derived from studies of non-neoplastic human disease as well as age-related phenotypic changes in human beta-cells.

We are determining the mechanisms of age-related decline in beta-cell function and replicative capacity, by mapping the changes in the beta-cell epigenome that occur with age. Selected genes will then be targeted using cutting-edge and emerging technologies such as Crispr-activation and inhibition systems that are already established or are being developed in our laboratories. The research team combines clinical experience with expertise in molecular biology and extensive experience in genomic modification aimed at enhancing beta-cell replication. By basing interventions on changes found in human disease and normal aging, this approach will increase the chances that discoveries made can be translated more rapidly into clinically relevant protocols.



RAHUL

KOHLI, M.D., PH.D.

*Assistant Professor of Medicine
and Biochemistry & Biophysics*

Lab Website

<https://sites.google.com/site/kohlilabsite/home>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20000220/p6341532>

Contact Information

University of Pennsylvania
502B Johnson Pavilion
3610 Hamilton Walk
Philadelphia, PA 19104-6073
Phone: 215-573-7523
Fax: 215-349-5111
Email: rkohli@pennmedicine.upenn.edu

Research Interest

In mammalian cells, DNA modifications are centered to the largest extent around cytosine bases, which are targeted by three different DNA modifying processes: methylation, oxidation and deamination. Research in the Kohli laboratory focused on the biochemistry and chemical biology of the enzymes that make cytosine such a dynamic base in the genome.

Cytosine methylation by DNA Methyltransferases (DNMTs) generates 5-methylcytosine (5mC), an epigenetic modification associated with silencing, while TET family enzymes can catalyze step-wise oxidation of 5mC to generate three new oxidized 5mC bases (ox-mCs) – 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC). These bases that are critical intermediates in the cycle of DNA demethylation and can also potentially serve as independent epigenetic marks. Deamination of either cytosine or modified cytosine bases by AID/APOBEC family enzymes yields targeted transition mutations in the genome. ‘Purposeful’ mutation by AID/APOBECs is used to garble foreign genomes, is exploited by the immune system to mature antibody responses, and has been posited to play roles in DNA demethylation. Such activity also carries risks and, accordingly, the deamination signatures of AID/APOBECs have been prominently left on cancer genomes.

In the Kohli laboratory, we utilize a broad array of approaches, which include: 1) biochemical characterization of enzyme mechanisms, 2) chemical synthesis of enzyme probes, and 3) biological assays spanning epigenetics and immunology to study DNA modifying enzymes.



ERICA KORB, PH.D.

*Assistant Professor
of Genetics*

Lab Website

<https://www.korblab.com>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Genetics
9-133 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
ekorb@pennmedicine.upenn.edu

Research Interest

The Korb lab works at the intersection of neuroscience and epigenetics. Epigenetic regulation is extremely important in neuronal function and contributes to the creation of new memories, our ability to adapt to our environment, and numerous neurological disorders. We try to understand how the world around us can influence gene expression in our neurons to allow us to learn, adapt, and become the people we are today.

In the lab, we focus on chromatin and its role in neuronal function. Chromatin is the complex of DNA and proteins called histones, which package our DNA into complex structures and control access to our genes. To study the role of histones in neuronal function and in disorders such as autism, we combine methods such as microscopy, bioinformatics, biochemistry, behavioral testing, and more. We have multiple areas of research in the lab, all focused on the study of chromatin and how it regulates neuronal function and neurodevelopmental disorders.



**MITCHELL A.
LAZAR, M.D., PH.D.**

*Willard and Rhoda Ware
Professor in Diabetes and
Metabolic Diseases; Director,
Institute for Diabetes, Obesity,
and Metabolism; Chief, Division
of Endocrinology, Diabetes,
and Metabolism*

Lab Website

<http://www.med.upenn.edu/lazarlab/director.html>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g20001500/p7505>

Contact Information

University of Pennsylvania
Division of Endocrinology, Diabetes & Metabolism
12-102 Smilow Translational Research Center
3400 Civic Center Boulevard
Philadelphia, PA 19104-5160
Tel: (215) 898-0198
Fax: (215) 898-5408

Research Interest

My laboratory focuses on the transcriptional and epigenomic regulation of metabolism by nuclear receptors and their coregulators. Our identification of the nuclear heme receptor Rev-erba and its corepressor complex, including histone deacetylase 3 (HDAC3), have uncovered fundamental principles of molecular

clocks and the circadian regulation of metabolism, as well as the tissue-specificity of coregulator function and epigenomic modifications. Our pioneering studies of PPAR γ and adipocyte biology, including discovery of the hormone resistin, have linked basic mechanisms of gene transcription to physiology and metabolic diseases. This work has important implications for endocrinology, diabetes, and metabolism.



MIA LEVINE, PH.D.

Assistant Professor of Biology

Lab Website

<http://web.sas.upenn.edu/levine-lab>

Faculty Website

<https://www.bio.upenn.edu/people/mia-levine>

Contact Information

University of Pennsylvania School of Arts and Sciences
Department of Biology
204B Carolyn Lynch Laboratories
433 South University Avenue
Philadelphia, PA 19104-6018
Office: 215-573-9709
m.levine@sas.upenn.edu

Research Interest

Chromatin proteins package our genomic DNA. Essential, highly conserved cellular processes rely on this genome compartmentalization, yet many chromatin proteins are wildly unconserved over evolutionary time. We study the biological forces that drive chromatin protein evolution and the functional consequences for chromosome segregation, telomere integrity, and genome defense.



**RONEN
MARMORSTEIN, PH.D.**

*Professor, Department of
Biochemistry and Biophysics
Investigator, Abramson Family
Cancer Research Institute*

Faculty Website

<https://www.chem.upenn.edu/profile/ronen-marmorstein>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Biochemistry and Biophysics
454 BRB II/III
421 Curie Blvd, Philadelphia, PA 19104-6161
Office: 215-898-7740
Fax: 215-746-5511
marmor@upenn.edu

Research Interest

The Marmorstein laboratory uses a broad range of molecular, biochemical and biophysical research tools centered around X-ray crystal structure determination to understand the chemical basis for the epigenetic regulation of gene expression. The laboratory is particularly interested in gene regulatory proteins and their upstream signaling kinases that are aberrantly regulated in cancer and other

age-related disorders such as obesity and Alzheimer's disease, and the use of high-throughput small molecule screening and structure-based design strategies towards the development of protein-specific small-molecule probes of protein function and for development into therapeutic agents.



JENNIFER E. PHILLIPS-CREMINS, PH.D.

*Assistant Professor of
Bioengineering; New York
Stem Cell Foundation –
Robertson Investigator*

Lab Website

<http://creminslab.com>

Faculty Website

<http://www.seas.upenn.edu/directory/profile.php?ID=187>

Contact Information

Department of Bioengineering
School of Engineering and Applied Sciences
University of Pennsylvania
210 South 33rd Street
Lab: 240 Skirkanich Hall
Office: 304 Hayden Hall
Philadelphia, PA 19104
Office: 215.898.4121
jcremins@seas.upenn.edu

Research Interest

Epigenomics and Systems Neurobiology Lab: The Cremins Lab investigates the link between three-dimensional organization of genomes and the establishment and maintenance of neural cell function. We employ systems level experimental and computational approaches to (1) create high-resolution 3-D genome architecture maps and (2) integrate 3-D architecture maps with genome-wide maps of epigenetic modifications and gene expression. Current work is focused on understanding the role for higher-order chromatin organization during differentiation of embryonic stem cells into neurons, during reprogramming of neurons into induced pluripotent stem cells and in models of neurodegenerative disease.



ARJUN RAJ, PH.D.

*Assistant Professor of
Bioengineering*

Lab Website

<http://rajlab.seas.upenn.edu>

Faculty Website

<https://www.seas.upenn.edu/directory/profile.php?ID=141>

Contact Information

University of Pennsylvania
School of Engineering and Applied Science
210 South 33rd St.
Philadelphia PA 19104-6321
Office: 215-898-7246
arjunrajlab@gmail.com

Research Interest

Our lab aims to develop a quantitative understanding of the molecular biology of the cell. Interests include chromosome structure and gene expression, non-coding RNA, and global regulation of gene expression. Applications include genetics, cancer and stem cells.



KAVITHA SARMA, PH.D.

*Assistant Professor, Gene
Expression and Regulation
Program (Wistar)*

Lab Website

<https://wistar.org/our-scientists/kavitha-sarma>

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g20000320/p8916652>

Contact Information

The Wistar Institute, Rm 232
Gene Expression & Regulation Program
3601 Spruce St, Philadelphia PA 19104
Tel: 215-898-3872
ksarma@wistar.org



JUNWEI SHI, PH.D.

*Assistant Professor of Cancer
Biology, Assistant Investigator
of Abramson Family Cancer
Research Institute*

Faculty Website

<http://www.cbio.med.upenn.edu/bioTemplate.asp?pageID=16>

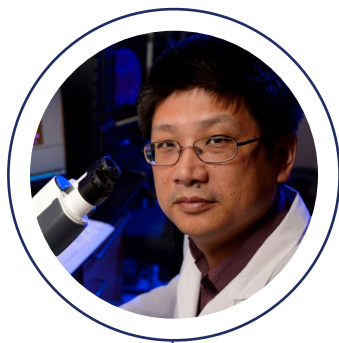
Contact Information

421 Curie Blvd
610 BRB II/III
Philadelphia , 19104-6160
Office: 215-746-5733
Fax: 215-573-6725
jushi@pennmedicine.upenn.edu

Research Interest

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, and causes up to 800,000 deaths annually worldwide. My lab focuses on understanding molecular pathways that support HCC growth. A major clinical challenge for HCC is that most patients are diagnosed at advanced stages, and no curative treatments are currently available. The multikinase inhibitor Sorafenib is the only approved therapy for late stage HCC, which confers only an approximately 3-month median survival benefit.

Current areas of interest within the lab include: (1) Defining the functional importance of epigenetic regulators in HCC, (2) Dissecting the signal transduction pathways that are required for HCC maintenance, and (3) Developing new functional genomic tools.



HONGJUN SONG, PH.D.

Professor of Neuroscience

Lab Website

<http://www.med.upenn.edu/songlab>

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g275/p8945425>

Contact Information

Perelman School of Medicine
Department of Neuroscience
415 Curie Blvd, Suite 111B
1st Floor Clinical Research Building
Philadelphia, PA 19104
Office: 215-573-2449
Email: shongjun@pennmedicine.upenn.edu

Research Interest

Research in Dr. Hongjun Song's laboratory focuses on two core topics: (1) neural stem cell regulation and neurogenesis in the developing and adult mammalian brain and how these processes affect neural function; (2) epigenetic and epitranscriptomic mechanisms and their functions in the mammalian nervous system. The lab is also interested in addressing how dysfunction of these mechanisms may be involved in brain disorders.



**GOLNAZ
VAHEDI, PH.D.**

*Assistant Professor of
Genetics, Member of Institute
for Immunology*

Lab Website

<http://vahedilab.github.io/LabSite>

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g20001881/p8837265>

Contact Information

310 Biomedical Research Building II/III
421 Curie Boulevard
Philadelphia, PA 19104
Office: 215-898-8439
Email: vahedi@pennmedicine.upenn.edu

Research Interest

The Vahedi laboratory is multidisciplinary, integrating computational and experimental approaches to develop a single to collective cell understanding of gene regulation in immune cells in health and disease.

We exploit the epigenomics mapping of immune cells to understand the biological circuits that underlie immune responses and uncover the molecular basis of major inherited diseases mediated by these cells. Immune-mediated disorders such as psoriasis and type 1 diabetes result from a complex interplay of genetic and environmental factors. By mapping the epigenomic alterations associated with immune-mediated diseases, we aim to further our understanding of the role of environment in triggering autoimmunity.

Information encoded in DNA is interpreted, modified, and propagated as chromatin. The diversity of inputs encountered by immune cells demands a matching capacity for transcriptional outcomes provided by the combinatorial and dynamic nature of epigenetic processes. Advances in genome editing and genome-wide analyses have revealed unprecedented complexity of chromatin pathways involved in the immune response, offering explanations to long-standing questions and presenting new challenges.

We blend epigenomics, human genetics, immunology, and computational biology to pursue a new understanding of human immunology. We generate genome-wide maps of chromatin in relevant immune cells mostly T cells. We are interested in regulators of T cell development and also T cell engagement in autoimmune disorders such as psoriasis and type 1 diabetes. We use population-based assays with strong signal-to-noise ratios such as ChIP-seq, ATAC-seq, and RNA-seq in addition to cutting-edge single-cell assays such as single-cell (sc)ATAC-seq and scRNA-seq. As a result of our computational expertise, we also harvest the vast troves of big data that immunologists and other researchers are pouring into public repositories. Our data integrations rely on available computational pipelines. Furthermore, we develop novel computational techniques to fully understand the complexity of multidimensional epigenomics datasets in T cells.



DORIS WAGNER, PH.D.

*Professor of Biology and
Graduate Chair in Biology*

Lab Website

<http://web.sas.upenn.edu/wagner-lab>

Faculty Website

<http://www.bio.upenn.edu/people/doris-wagner>

Contact Information

University of Pennsylvania School of Arts and Sciences
Department of Biology
103G Carolyn Lynch Laboratory
Philadelphia, PA 19104
Office: 215-898-0483
wagnerdo@sas.upenn.edu

Research Interest

Our research focuses on the reprogramming of cell identity and function during developmental transitions and in response to environmental inputs in plants. These sessile organisms are an excellent experimental system to address this question as they tailor their final form and cell function to a changing environment to optimize growth and survival. We have shown that master transcriptional regulators, hormone response and chromatin state together orchestrate cell fate reprogramming in plants.



**MATT
WEITZMAN, PH.D.**

*Professor of Pathology and
Laboratory Medicine*

Lab Website

<http://www.chop.edu/cccr/labs/matthew-weitzman-laboratory>

Faculty Website

<http://pathology.med.upenn.edu/departments/people/517/matthew-d-weitzman>

Contact Information

4050 Colket Translational Research Building
The Children's Hospital of Philadelphia Research Institute
3501 Civic Center Blvd
Philadelphia, PA 19104
Office: 267-425-2068
weitzmanm@email.chop.edu

Research Interest

Our lab aims to understand host responses to virus infection, and the cellular environment encountered and manipulated by viruses. We study multiple viruses

in an integrated experimental approach that combines biochemistry, molecular biology, genetics and cell biology. We have chosen viral models that provide tractable systems to investigate the dynamic interplay between viral genetic material and host defense strategies. We have used proteomic approaches to probe the dynamic interactions that take place on viral and cellular genomes during infection, and have uncovered ways that viruses manipulate histones and chromatin as they take control of cellular processes. The pathways illuminated are key to fighting diseases of viral infection, provide insights into fundamental processes that maintain genome instability, and have implications for the development of efficient viral vectors for gene therapy.



HAO WU, PH.D.

Assistant Professor of Genetics

Faculty Website

<https://www.med.upenn.edu/apps/faculty/index.php/g275/p8878781>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Genetics
547A Clinical Research Building
415 Curie Blvd
Philadelphia, PA 19104-6145
Office: 215-573-9360
haowu2@penntmedicine.upenn.edu

Research Interest

DNA cytosine methylation (5-methylcytosine) is an evolutionarily conserved epigenetic mark and has a profound impact on transcription, development and genome stability. Historically, 5-methylcytosine (5mC) is considered as a highly stable chemical modification that is mainly required for long-term epigenetic memory. The recent discovery that ten-eleven translocation (TET) proteins can iteratively oxidize 5mC in the mammalian genome represents a paradigm shift in our understanding of how 5mC may be enzymatically reversed. It also raises the possibility that three oxidized 5mC bases generated by TET may act as a new class of epigenetic modifications.

Our laboratory uses high-throughput sequencing technologies, bioinformatics, mammalian genetic models, as well as synthetic biology tools to investigate the mechanisms by which proteins that write, read and erase oxidized 5mC bases contribute to mammalian development (particularly cardiovascular and neural lineages) and relevant human diseases. To achieve this goal, we are also interested in developing new genomic sequencing and programmable epigenome-modifying methods to precisely map and manipulate these DNA modifications in the complex mammalian genome.



**KENNETH S.
ZARET, PH.D.**

*Joseph Leidy Professor
Director, Institute for
Regenerative Medicine*

Lab Website

zaretlab.med.upenn.edu

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g306/p4485296>

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9-131 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-573-5813
Lab: 215-573-5844
zaret@upenn.edu

Research Interest

Ken's laboratory discovered "pioneer factors" that bind to silent chromatin, endow the competence for cell differentiation, and promote cellular reprogramming. Recently, his lab found broad chromatin domains that can resist pioneer factor binding and serve as impediments to cellular reprogramming; these domains appear to help commit cells to particular fates. Finally, his lab has unveiled how inductive signaling in the embryo leads to chromatin modifications that affect cell fate choices, thereby identifying specific enzymatic targets for small molecules to modulate cell fate control.



**ZHAOLAN (JOE)
ZHOU, PH.D.**

*Associate Professor
of Genetics*

Lab Website

<http://www.med.upenn.edu/zhoulab/#>

Faculty Website

<http://www.med.upenn.edu/apps/faculty/index.php/g306/c404/p8330052>

Contact Information

Department of Genetics
University of Pennsylvania School of Medicine
452A Clinical Research Building
415 Curie Blvd
Philadelphia, PA 19104-6145
Tel: 215-746-5025
Fax: 215-573-7760
zhaolan@penmedicine.upenn.edu

Research Interest

A fundamental question in Genetics and Neuroscience is how the brain executes genetic programs while maintaining the ability to adapt to the environment. The underlying molecular mechanisms are not well understood, but epigenetic regulation, mediated by DNA methylation and chromatin organization, provides an intricate platform bridging genetics and the environment, and allows for the integration of intrinsic and environmental signals into the genome and subsequent translation of the genome into stable yet adaptive functions in the brain. The goal of the Zhou lab is to identify and understand the epigenetic principles that integrate environmental factors with genetic code to govern neural network formation and function in the brain, and to determine how defects in this process may lead to intellectual disability.



BIOINFORMATICIAN



YEMIN LAN, PH.D., *Bioinformatician*

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9-155 Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-573-7215

If you would like to work with Yemin, please contact her to set up a meeting:
yeminlan@mail.med.upenn.edu

If it turns out that she can be of help to you, you will then be required to fill out a request for approval: <http://bic.ibi.upenn.edu/service/request.html>

Research interest/work responsibility

My role in the Epigenetics Program is to provide bioinformatic services. This includes analysis of big data and next-generation sequencing data in particular, consultation and education of computational topics of interest.



MAGGIE SHAW, PSM, *Genomic Data Coordinator, Junior Bioinformatician*

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9th Floor Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059

Research interest/work responsibility

Responsibility is to provide bioinformatics services for the Epigenetics Institute. Often, services involving the analysis of next-generation sequencing data and large genomic data sets.



ADMINISTRATION

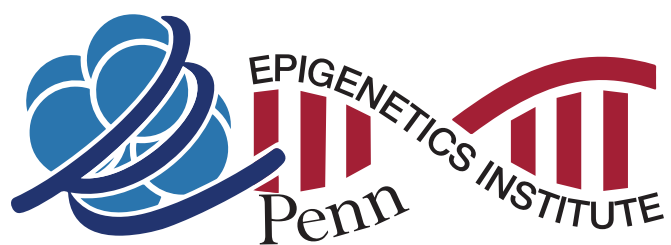


SOPHIA CASTRO-ANDERSON, MBA

Administrator for the Epigenetics Institute.

Contact Information

The Perelman School of Medicine at the University of Pennsylvania
Department of Cell and Developmental Biology
9-130A Smilow Center for Translational Research
3400 Civic Center Blvd
Philadelphia, PA 19104-6059
Office: 215-573-5858
andes@pennmedicine.upenn.edu



<https://hosting.med.upenn.edu/epigenetics>