Northwestern Medicine®
Feinberg School of Medicine

6th Simpson Querrey Institute for Epigenetics Symposium

October 25, 2024

"Cancer Epigenetics"

SQE

AGENDA - MORNING SESSION

8:30 AM	-	9:00 AM	Breakfast
9:15 AM	-	9:30 AM	Welcome and Introduction: Ali Shilatifard, Director, Simpson Querrey Institute for Epigenetics

MORNING SESSION 1 9:15 AM – 10:50 AM
Session Chair: Lu Wang, PhD, Northwestern University

9:30 AM	-	9:50 AM	Shelley Berger, PhD, University of Pennsylvania *"Epigenetic pathways as targets in human disease"*
9:50 AM	-	10:10 AM	Dylan Taatjes, PhD, University of Colorado, Boulder *"Clinically relevant CDK7 inhibitors reveal mechanistic insights"*
10:10 AM	-	10:30 AM	Emma Farley, PhD, University of California, San Diego *"Enhancer syntax encodes tissue-specificity"*
10:30 AM	-	10:50 AM	Karen Adelman, PhD, Harvard School of Medicine *"Understanding enhancer-mediated control of gene activity"*
10:50 AM	-	11:35 AM	Coffee Break

MORNING SESSION 2 11:35 AM – 12:35 PM
Session Chair: Andrea Piunti, PhD, University of Chicago

11:35 AM	-	11:55 AM	Karim-Jean Armache, PhD, NYU *"Molecular mechanisms of epigenetic regulation"*
11:55 AM	-	12:15 PM	Cheryl Walker, PhD, Baylor College of Medicine *"Epigenetic aging as a target for developmental reprogramming by environmental exposures"*
12:15 PM	-	12:35 PM	Laura Pasqualucci, MD, Columbia University *"Differential role of CREBBP missense and truncating mutations in instructing germinal center B cell fates to initiate lymphomagenesis"*
12:35 PM	-	2:00 PM	Lunch break

AGENDA – AFTERNOON SESSION

AFTERNOON SESSION 1 2:00 PM – 3:20 PM
Session Chair: Shannon Lauberth, PhD, Northwestern University

2:00 PM	-	2:20 PM	Lu Wang, PhD, Northwestern University *"Molecular dissection of the gene essentiality and transcriptional reprogramming in cancer"*
2:20 PM	-	2:40 PM	Julien Sage, PhD, Stanford University *"Intra- and inter-tumoral heterogeneity in small cell lung cancer progression and metastasis"*
2:40 PM	-	3:00 PM	Zibo Zhao, PhD, Northwestern University *"MLL4/COMPASS dysfunction in cancer and treatment"*
3:00 PM	-	3:20 PM	Andrea Piunti, PhD, University of Chicago *"CATACOMB prevents PRC2 mediated transcriptional repression upon DNA hypomethylation"*
3:20 PM	-	4:00 PM	Coffee Break

AFTERNOON SESSION 2 4:00 PM –5:00 PM
Session Chair: Zibo Zhao, PhD, Northwestern University

4:00 PM	-	4:20 PM	Yadira Soto-Feliciano, PhD, MIT *"Mechanisms of gene regulation and dysregulation by chromatin adaptors"*
4:20 PM	-	4:40 PM	Yang Shi, PhD, University of Oxford *"Chromatin regulation in human diseases"*
4:40 PM	-	5:00 PM	Closing Remarks: Lu Wang and Andrea Piunti

KAREN ADELMAN, PH.D.

Edward S. Harkness Professor of Biological Chemistry
and Molecular Pharmacology, Blavatnik Institute
Harvard Medical School, Boston

Dr. Karen Adelman is the Edward S. Harkness Professor of Biological Chemistry and Molecular Pharmacology at Harvard Medical School. She is a member of the Gene Regulation Observatory at the Broad Institute, and the Ludwig Cancer Center at Harvard Medical School. Dr. Adelman has been elected to the American Academy of Arts and Sciences and EMBO.

The Adelman lab pioneered genomic studies of RNA polymerase II (RNAPII) transcription, revealing that pausing of RNAPII in early elongation is a central regulatory step in metazoan gene expression. Ongoing work probes the interplay between transcription, RNA processing and epigenetic machineries to elucidate the determinants of mature mRNA formation in health and disease.

"UNDERSTANDING ENHANCER-MEDIATED CONTROL OF GENE ACTIVITY"

I will discuss our work towards understanding what makes promoters dependent on regulation by enhancers, and how chromatin modifying complexes work to stimulate enhancer activity.

KARIM JEAN ARMACHE, PH.D.

Professor, Department of Biochemistry and Molecular Pharmacology, NYU, Grossman School of Medicine

Dr. Karim-Jean Armache is a Professor of Biochemistry and Molecular Pharmacology at NYU Grossman School of Medicine, specializing in transcription, chromatin biology, and epigenetics. His group focuses on mechanistic chromatin biology, using structural, biochemical, and cell biology techniques. His early work includes determining the first structure of a complete initiation-competent RNA Pol II and the first structure of the gene-silencing factor bound to the nucleosome. His research group has since elucidated the structures of chromatin modifiers on nucleosomes with various histone modifications and explored non-catalytic mechanisms of histone lysine methyltransferases. Additionally, they have advanced the understanding of viral chromatin, demonstrating how viral nucleosomes organize chromatin inside giant viruses. Dr. Armache's work has clarified the interactions between histone modifications and the complexes that modify them, provided insights into Trithorax and Polycomb Group enzyme functions, and explored the impact of these processes on gene expression in diseases like cancer. His research also has potential applications in developing targeted therapies for epigenetic disorders. For his contributions, Dr. Armache has received several recognitions, including the Kimmel Cancer Scholar award in 2014, the Packard Fellowship for Science and Engineering in 2015, and the Mark Foundation Emerging Leader in Cancer Award in 2022.

"MOLECULAR MECHANISMS OF EPIGENETIC REGULATION"

Tight regulation of gene activation and silencing is critical to normal development. The Polycomb Group (PcG) and Trithorax Group (TrxG) chromatin-modifying protein complexes establish the essential and complex system that maintains gene expression programs in mammals, disruption of which is a major cause of developmental disorders and cancer. PcG complexes silence genes by creating a chromatin environment restrictive to transcription, and TrxG complexes activate genes by facilitating transcription through chromatin. The balance between these two counteracting groups of proteins regulates chromatin at multiple levels, from its local structure to the three-dimensional organization of the genome. The functional diversity of both PcG and TrxG complexes is thought to arise through their modular compositions and distinct enzymatic and non-enzymatic properties. However, understanding how they catalyze different histone modifications and generate structural changes that compact or open chromatin remains a fundamental challenge for biology and medicine. Our research program aims to gain a detailed molecular understanding of the basic mechanisms and complex interplay of gene silencing and activating complexes. These studies inform basic, fundamental knowledge of protein complexes critical for chromatin regulation, while offering new avenues to develop therapeutics that target their aberrant functions in diseases such as cancer. I will discuss our progress in understanding the mechanisms and roles of key PcG and TrxG complexes involved in chromatin modification and gene regulation.

SHELLEY BERGER, PH.D.

Professor, University of Pennsylvania
Departments of Cell & Developmental Biology, Genetics, Biology
Director, Epigenetics Institute, Penn Perlman School of Medicine

Shelley Berger PhD is the Daniel S. Och University Professor at the University of Pennsylvania and previously held the Hilary Koprowski Professorship at the Wistar Institute in Philadelphia. Dr. Berger serves as director of the Epigenetics Institute in the Penn Perelman School of Medicine. Dr. Berger earned her PhD from University of Michigan and was a post-doctoral fellow at Massachusetts Institute of Technology. She was awarded the Penn Medicine Cohen Biomedical Research Award and the Penn Biomedical Postdoctoral Distinguished Mentor Award. She has >30 years of experience in mentoring and training graduate students and postdoctoral fellows, now successful in careers in academia, pharmaceutical industry, scientific writing, and teaching. Dr. Berger is committed to improving academic training for graduate students and postdocs; in 2023 she initiated and co-led a Working Group for the Advisory Committee to the NIH Director, "Re-envisioning Postdoctoral Training in US Biomedicine".

Dr. Berger is an elected fellow of the National Academy of Sciences, National Academy of Medicine, American Association of Cancer Research, Academy of Healthspan and Lifespan Research,, and American Academy of Arts and Sciences. Her work over thirty years helped to launch the modern era of chromatin biology and epigenetics. Her discoveries provided a paradigm for mechanisms of histone and factor modifying enzymes in gene regulation. Recent research revealed a vital role of histone and factor modifications in aging and senescence, cancer, mammalian memory and Alzheimer's disease, as well as revealing a decisive role underlying organismal level behavior and aging in ant models of complex sociality.

"EPIGENETIC PATHWAYS AS TARGETS IN HUMAN DISEASE"

Chromatin regulatory proteins are frequently mutated or overexpressed in human disease. Because they are enzymes, chromatin proteins are outstanding targets for drug development. Our work focuses on elucidation of epigenetic pathways that might be disease drivers, and epigenetic pathways that might augment clinical treatment.

Our work in cancer focuses on epigenetic pathways utilized by the tumor suppressor p53 and oncogene HIF2alpha; we also study epigenetics of cancer immunotherapy pathways of active and exhausted T cells. In addition, we investigate epigenetics of aging and in regulation of mouse and human memory and diseases of memory, including human Alzheimer's disease. Aspects of these epigenetic regulatory pathways will be discussed.

EMMA FARLEY, PH.D.

Assistant Professor, Department of Molecular Biology
University of California, San Diego

Emma Farley is Assistant Professor at the University of California, San Diego. Her lab use high-throughput functional approaches within developing embryos to decipher how enhancers encode the instructions for successful development and to pinpoint enhancer mutations associated with disease. She received her Bachelor's and Master's in Biochemistry from Oxford University and a Ph.D. in Developmental Biology from Imperial College London. Emma worked in Mike Levine's lab at UC Berkeley and Princeton University as a postdoc, where she exploited the advantages of the model organism Ciona intestinalis (the sea squirt) for functional genomics. She developed methods to create and functionally test millions of enhancer variants in every cell of a developing embryo. Her research enabled the first high-throughput dissection of an enhancer within whole developing embryos, these studies revealed regulatory principles governing enhancer function.

Homepage: https://farleylab.com/
LinkedIn: https://www.linkedin.com/in/emma-farley-72034295
Twitter: https://twitter.com/ekfarley?lang=en

"ENHANCER SYNTAX ENCODES TISSUE-SPECIFICITY"

Enhancers direct precise patterns of gene expression during development by interactions with transcription factors (TFs)1,2. To explore how the organization of transcription factor binding sites (TFBSs) within enhancers encodes this precision, we conducted a high-throughput screen testing 460,800 different organizations of ETS and GATA TFBSs for activity within developing embryos. We provide evidence that enhancer-specificity depends on the functional organization, or syntax, of TFBSs. Optimal syntax of TFBSs mediates robust but ectopic patterns of gene expression. Multiple overlapping syntax features within an enhancer encode activity. Too many syntax features, or individual syntax features that are too optimal, lead to loss of specificity. Tissue-specific enhancers have less optimal syntax, which is permissive to transcription but is dependent on the affinity of TFBSs. Enhancer grammar3, the interplay of sub-optimal syntax and affinity, encodes tissue-specificity. We use this grammatical principle to predict genomic enhancers and design synthetic enhancers that drive precise gene expression in response to pleiotropic factors. Our study uncovers how the complex language of enhancers encodes tissue-specificity, with far reaching applications for reading and writing gene expression.

LAURA PASQUALUCCI, M.D.

Professor, Pathology & Cell Biology, Institute for Cancer Genetics
Columbia University, NYC

Laura Pasqualucci, MD, is a Professor of Pathology and Cell Biology in the Institute for Cancer Genetics, Columbia University. Her research over the last 25 years has focused on the identification and functional characterization of genetic lesions implicated in the pathogenesis of B cell lymphomas, including their in vivo modeling, with the ultimate goal of identifying better biomarkers and more effective treatment options for these diseases. Her work has provided significant contributions to the current understanding of the two most common forms of lymphoid malignancies, follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL), by identifying multiple lymphoma-driving genetic lesions in these cancers and demonstrating the role these genes play in both normal germinal center (GC) biology and the malignant transformation process.

Together with Dr. Dalla-Favera, she discovered that the AID-driven somatic hypermutation (SHM) process can introduce mutations outside the immunoglobulin loci, including the recent identification of a pervasive aberrant SHM activity that specifically targets super-enhancer networks in DLBCL. Following the discovery of recurrent inactivating mutations of histone/chromatin modifiers in FL and DLBCL, including the methyltransferase KMT2D and the acetyltransferases CREBBP/EP300, her laboratory has been focusing on elucidating the mechanisms by which these alterations perturb the epigenetic landscape of GC B cells to facilitate their clonal expansion. These studies established a role for histone modifier genes as bona-fide tumor suppressors in GC-derived lymphoma, which are disrupted as early events during the history of tumor clonal evolution. This information is currently being exploited for the development of targeted therapeutic approaches in these diseases.

"DIFFENTIAL ROLE OF *CREBBP* MISSENSE AND TRUNCATING MUTATIONS IN INSTRUCTING GERMINAL CENTER B CELL FATES TO INITIATE LYMPHOMAGENESIS"

Somatic mutations of the CREBBP acetyltransferase and the KMT2D methyltransferase are highly recurrent in germinal center (GC)-derived lymphomas, including follicular lymphoma (FL, 60-80% of cases) and diffuse large B cell lymphoma (DLBCL; 40-60% of cases in the EZB/C3 subtype). Mutations include prototypical inactivating events that abrogate the protein C-terminal enzymatic domains, as well as amino-acid changes clustering within these domains, which impair the protein enzymatic activity (Pasqualucci et al., *Nature* 2011; Zhang et al., Nature Medicine 2015). Notably, these events are acquired early during lymphomagenesis, in a putative common precursor cell (CPC) that subsequently undergoes divergent evolution to FL or tFL through the acquisition of additional genetic lesions. Consistently, we have shown in vivo that CREBBP and KMT2D act as haplo-insufficient tumor suppressors, the loss of which accelerates the development of *BCL2* translocation-driven lymphomas and synergize with each other to disrupt enhancer networks implicated in the control of terminal B cell differentiation and of B:T cell interactions with the immune microenvironment. While extensive work has focused on understanding the lymphoma-driving role of CREBBP protein loss, mimicking the outcome of truncating mutations, the functional

significance of missense mutations remains largely unexplored. This is a critical gap because, different from truncated proteins, CREBBP missense mutants are expressed, suggesting they may contribute to malignant transformation through distinct mechanisms. In support of this view, missense and truncating mutations are differentially distributed in FL and DLBCL, with the former being preferentially enriched in FL (p<0.01).

This presentation will focus on recent data revealing shared but also unique functions of missense mutations affecting the CREBBP acetyltransferase domain, as obtained by taking advantage of a novel mouse model for the GC-specific expression of the recurrent R1446H hotspot mutant allele (hereafter, Crebbp^{RH}). Specifically, we found distinct transcriptional and epigenetic changes separating *Crebbp^{RH} vs Crebbp^{KO}* GC B cells, with *Crebbp^{RH}* being positively enriched in light zone-associated and pre-memory B cell differentiation programs, while these signatures were negatively regulated upon *Crebbp* deletion. Accordingly, expression of *Crebbp^{RH}* led to a pronounced, dose-dependent pre-neoplastic expansion of GCs displaying an abnormal dark zone to light zone ratio, and persisting abnormally for several weeks after immunization, when the GC reaction is normally extinguished, indicating altered dynamics. Moreover, *Crebbp^{RH}* mice showed increased memory B cell responses to the T cell-specific antigen NP-KLH (p<0.01), which was not detected in *Crebbp^{KO}* mice, as measured by immunophenotyping. Finally, *Crebbp^{RH}* but not *Crebbp^{KO}* mice showed compositional changes in the T cell microenvironment, with expansion of T follicular helper cells (8.3%, vs 3.8% in WT mice; p<0.05). Thus, *Crebbp* missense mutations may skew GC B cell fate decisions toward memory B cell differentiation and favor the persistence of GCs to facilitate the malignant transformation process, in part by altering the GC microenvironment. These data have implications for the understanding of FL/DLBCL ontogeny and for the therapeutic targeting of tumors carrying missense vs truncating mutations.

ANDREA PIUNTI, M.S., PH.D.

Assistant Professor, Department of Pediatrics
The University of Chicago

Andrea Piunti is an Assistant Professor in the Department of Pediatrics at the University of Chicago. Dr. Piunti completed his PhD in Molecular Oncology at the European Institute of Oncology (IEO) in Diego Pasini's Lab in 2014. He then moved to Northwestern University where he joined, as a postdoctoral fellow, Ali Shilatifard's Lab where he was supported by the EMBO Long-Term fellowship, the Marie Curie Action/iCARE fellowship and the NCI/K99 transition to independence award.

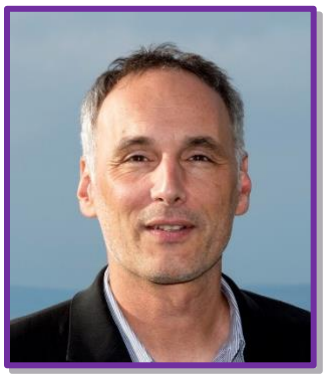
He started his independent career in 2021 as an Assistant Professor in the Division of hematology/oncology in the Department of Pediatrics at the University of Chicago where is currently supported by the NCI/R00 award.

Andrea and his Lab focus on chromatin biology and how its deregulation contributes to cancer onset and progression. His lab focuses on the Polycomb group (PcGs) of proteins, which are major chromatin regulators. PcG proteins are master regulators of mammalian development and cellular proliferation. They mainly exert their function through transcriptional repression achieved through their activity on chromatin. Several PcG proteins and their activities are deregulated in cancer, and they play particularly important roles in the oncogenic processes underlying rare pediatric brain tumors such as diffuse midline gliomas (DMG) and posterior fossa group A (PFA) ependymomas. Dr. Piunti works to understand how deregulation of PcG proteins in these tumors contributes to the insurgence and spreading of these and other rare malignancies.

"CATACOMB PREVENTS PRC2 MEDIATED TRANSCRIPTIONAL REPRESSION UPON DNA HYPOMETHYLATION"

The Polycomb Repressive Complex 2 (PRC2) is the unique multiprotein complex responsible for the di- and tri- methylation of the lysine 27 on histone H3 (H3K27me2/3). PRC2 activity is crucial for organismal development, and it is highly deregulated in a multitude of cancers. Recently, the CATAlytic Antagonist of polyCOMB (CATACOMB) was identified as the first PRC2 subunit that, when expressed, results in massive reduction of H3K27me2/3. *CATACOMB* is a monoexonic gene whose expression is restricted by DNA methylation deposited at the large CpG island that spans more than half of its length. We previously proposed CATACOMB as the major interlocutor between DNA methylation and PRC2 activity during acute DNA hypomethylation. We expand our observation using different hypomethylating agents (HMAs) and cells from different tissues to verify the broad significance of this mechanism. Importantly, CATACOMB is critical for preventing transcriptional silencing of a subset of genes that are activated by treatment with HMAs.

These genes are characterized by H3K27me3 around the promoter regions that is reduced upon treatment with HMA leading to subsequent transcriptional activation. The reduction of H3K27me3 and transcriptional activation of these genes are dependent on the concomitant expression of CATACOMB. Also, CATACOMB induced expression prevents PRC2 mediated transcriptional silencing of a subset of lowly expressed genes upon treatment with HMAs. This study elucidated the counteracting function of CATACOMB in PRC2 mediated transcriptional repression upon treatment with HMAs and might be relevant in understanding the way that HMAs work in patients. Additionally, this mechanism could be at the base of driving neoplastic events that characterize tumors with CATACOMB expression such as PFA ependymomas that are often characterized by global DNA hypomethylation.



JULIEN SAGE, PH.D.

Professor, Pediatrics and Genetics
Stanford University

Dr. Sage grew up in France. As a student at the École Normale Supérieure in Paris, he studied biology, and then did his PhD at the University of Nice with Dr. François Cuzin and his post-doctoral training at MIT with Dr. Tyler Jacks. He started his own research group at Stanford in 2004 where he is currently the Elaine and John Chambers Professor in Pediatric Cancer and a Professor of Genetics, and where he serves as the co-Director of the Cancer Biology PhD program. For his work on cancer genetics, he has been awarded a Damon Runyon Cancer Research Foundation Scholar Award, a Leukemia and Lymphoma Society Scholar Award, and an R35 Outstanding Investigator Award from the National Cancer Institute. Dr. Sage's work has focused on the RB tumor suppressor pathway and how inactivation of RB promotes tumorigenesis in children and adults.

Dr. Sage became initially interested in small cell lung cancer (SCLC) because of the nearly ubiquitous loss of RB in this cancer type and the intriguing relationship in mice and humans between loss of RB and the growth of neuroendocrine lesions. In the past few years, the Sage lab has developed pre-clinical models for SCLC, including genetically engineered mouse models, and has used these models to investigate signaling pathways driving the growth and metastatic ability of this cancer type and to identify novel therapeutic targets in this recalcitrant cancer.

"INTRA- AND INTER-TUMORAL HETEROGENEITY IN SMALL-CELL LUNG CANCER PROGRESSION AND METASTASIS"

Intra-tumoral heterogeneity and cancer cell plasticity are critical aspects of tumor growth, metastasis, and response to treatment in the clinic. We have used small cell lung cancer (SCLC) as a paradigm to reveal key cellular states and identify ways to target specific cell states and transition between these states during tumor development and metastasis. SCLC is the most fatal form of lung cancer. Standard-of-care is aggressive chemoradiation therapy combined with T-cell immune checkpoint inhibitors, but median survival still hovers around 10 months after diagnosis. SCLC is fast-growing and highly metastatic. SCLC patients are thus in dire need of new therapeutic options. SCLC is a neuroendocrine (NE) cancer that was historically considered very homogeneous, but accumulating evidence indicates that different subtypes of SCLC exist (inter-tumoral heterogeneity), and that intra-tumoral heterogeneity is prominent in SCLC tumors, with SCLC cells displaying a range of expression for NE markers and different cell proliferation potential. Mounting evidence further indicates that this heterogeneity is functionally important for tumor growth, metastasis, and response to therapy. We will discuss the mechanisms by which heterogeneity is generated in SCLC tumors. We will also illustrate how distinct SCLC cell states may be targeted in relevant pre-clinical models. A better understanding of heterogeneity in SCLC may eventually lead to novel therapeutic approaches in patients.

YANG SHI, PH.D.

Professor, University of Oxford
Ludwig Cancer Research Institute

Yang Shi received his PhD from NYU Medical Center and postdoctoral training with Dr. Tom Shenk at Princeton University where he discovered the transcription factor YY1. He began his independent research career at Harvard Medical School as a tenure track assistant professor in 1991 and received tenure and full professorship in the Department of Pathology at Harvard Medical School in 2004. In 2009 he joined Boston Children's Hospital where he held a Merton Bernfield Professorship in the Department of Medicine and was also professor of Cell Biology of Harvard Medical School, where he was honored with the inaugural C. H. Waddington Professorship of Pediatrics in 2018.

He joined Oxford University in 2020 and is currently Professor of Epigenetics of Oxford University and member of the Ludwig Cancer Research. His honors include election to the American Association for the Advancement of Science (2011), The Ellison Medical Foundation Senior Scholar in Aging (2012), American Cancer Society Research Professor (2012), election to the American Academy of Arts and Sciences (2016), election to EMBO (2022), to AACR Academy (2022), the National Academy of Medicine (2022) and UK Academy of Medical Sciences (2023).

"CHROMATIN REGULATION IN HUMAN DISEASES"

Genetic mutations and mis-regulation of epigenetic regulators are associated with human cancer. Consequently, drugs that target epigenetic regulators are being developed but toxicity represents a significant challenge. In this presentation, I will discuss our efforts of identifying synergizers of epi-drugs to mitigate toxicity and to improve efficacy.

YADIRA SOTO-FELICIANO, PH.D.

Assistant Professor, Biology Department
Koch Institute for Integrative Cancer Research at MIT

Dr. Yadira Soto-Feliciano is an Assistant Professor of Biology at MIT. She received a BS in Chemistry from the University of Puerto Rico at Mayagüez in 2008. She received a PhD in Biology from MIT in 2016. She conducted her doctoral work in the laboratory of Prof. Michael T. Hemann at the Koch Institute/MIT, where she combined mouse models of leukemia with in vivo functional genomics approaches to study mechanisms of cell identity and lineage plasticity. These studies, along with mounting evidence pointing to epigenetic alterations as a central mechanism behind human diseases like cancer, led her to pursue formal postdoctoral training in chromatin biology and epigenetic mechanisms. Prof. Soto-Feliciano completed her postdoctoral training at the Rockefeller University in the laboratory of Dr. David Allis in 2021.

During this period, she was supported by a Damon Runyon-Sohn Pediatric Cancer Fellowship and subsequently received an NIH/NIGMS K99/R00 award. Her postdoctoral work combined cancer biology and functional genomics with traditional chromatin biology and biochemistry, to understand the role of chromatin adaptor/scaffold proteins in cancer. She joined the MIT faculty in 2022 as an Assistant Professor in the Department of Biology and an intramural member of the Koch Institute. Her research group studies the molecular mechanisms underlying chromatin scaffolding-mediated transcriptional regulation. The overall goal of her research is to fill significant gaps in our understanding of chromatin regulation by shedding light on the context-dependent and often antagonistic roles that many chromatin regulators exhibit in development and disease and how they can be harnessed for rational design of targeted epigenetic therapies.

"MECHANISMS OF GENE REGULATION AND DYREGULATION BY CHROMATIN ADAPTORS"

Chromatin, the physiological form of our genome, is composed of DNA and histone proteins. Post-translational modifications of these components, along with their regulatory factors, are essential for maintaining cellular integrity, tissue health, and the overall functioning of organisms. Large-scale sequencing efforts have revealed that alterations in chromatin and epigenetic regulators are commonly associated with human diseases, including developmental disorders and cancers. While significant attention has been directed toward understanding chromatin-modifying enzymes and their dysregulation in disease, less is known about the role of chromatin adaptor/scaffold proteins, which assemble these enzymatic complexes. Our research focuses on this underexplored area, particularly the catalytic-independent activities and scaffolding functions of chromatin-modifying enzymes. By leveraging our expertise in cancer biology and chromatin biochemistry, we investigate how chromatin adaptors decode chemical signals and regulate gene expression in both healthy and diseased states. One such adaptor, TRIM28 (KAP-1), has been identified as a key regulator of heterochromatin formation and cellular differentiation. Our recent studies have uncovered TRIM28 as an essential epigenetic regulator in acute myeloid leukemia (AML). Inhibiting TRIM28, either biochemically or genetically, significantly reduces leukemia cell proliferation in vivo, accompanied by changes in gene expression, including the upregulation of neutrophil-

associated transcriptional programs. These findings suggest that TRIM28 functions as a dual transcriptional regulator, modulating gene expression through its context-specific interactions with proteins and chromatin. The scaffolding function of TRIM28 underscores its potential as a novel therapeutic target in AML treatment, with further research poised to advance targeted leukemia therapies and broaden clinical intervention strategies.

DYLAN TAATJES, PH.D.

Professor, Biochemistry
University of Colorado, Boulder

Dylan Taatjes studied chemistry as an undergraduate and got his PhD in organic chemistry from the University of Colorado, Boulder, in the lab of Dr. Tad Koch. His PhD work uncovered the mechanism of action of anthracycline anti-tumor drugs that remain widely used in the clinic. During his PhD, Dr. Taatjes became fascinated with transcription and cancer biology and decided to transition away from chemistry for his postdoctoral studies, in part because it was apparent that many more discoveries would be made in the biological and biomedical sciences compared with organic chemistry. He worked at the interface of molecular biology, biochemistry, and structural biology during his postdoctoral studies with Dr. Robert Tjian and Dr. Eva Nogales at the University of California, Berkeley.

Dr. Taatjes joined the faculty at UC-Boulder in 2004 and is currently a Professor in the Department of Biochemistry. His research interests include cell signaling and the regulation of gene expression, with an emphasis on molecular mechanisms and biochemical reconstitution of human RNA polymerase II transcription.

"CLINICALLY RELEVANT CDK7 INHIBITORS REVEAL MECHANISTIC INSIGHTS"

A focus of the Taatjes lab is the regulation of RNA polymerase II (pol II) function in human cells. The so-called Pre-Initiation Complex (PIC) controls pol II function at transcription start sites; the PIC consists of Mediator, pol II, TFIIA, TFIIB, TFIID, TFIIE, TFIIF, and TFIIH and is approximately 4.0 MDa in size. Broadly speaking, the PIC functions to regulate the activity of the pol II enzyme, which transcribes all protein-coding genes and most non-coding RNAs in the human genome. Within the PIC, the 1.4 MDa Mediator complex, the 1.3 MDa TFIID complex, and the 0.5 MDa TFIIH complex help regulate pol II activity in ways that remain poorly understood. At a basic level, TFIIH regulates transcription initiation and post-initiation steps (e.g., RNA processing), whereas Mediator and TFIID function by converting biological inputs (communicated by sequence-specific, DNA-binding transcription factors) to physiological responses (via changes in gene expression). Many additional factors contribute pol II function, including transcription-associated kinases such as CDK7, CDK8, and CDK9. During my seminar, I will discuss how our lab uses next-generation kinase inhibitors, biochemistry, transcriptomics, and other approaches to address basic mechanistic questions about how CDK7, a TFIIH-associated kinase, regulates gene expression and proliferation in human cells.

CHERYL WALKER, PH.D.

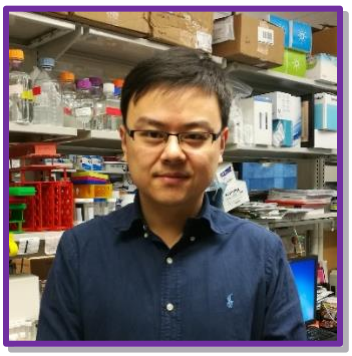
Director, Center for Precision Environmental Health
Baylor College of Medicine

Dr. Cheryl Lyn Walker, Ph.D. is the Director of the Center for Precision Environmental Health at Baylor College of Medicine, where she holds the Alkek Presidential Chair in Environmental Health and is a Professor in the departments of Molecular & Cell Biology, Medicine, and Molecular & Human Genetics. In 2016 she was elected to the National Academy of Medicine and has been recognized with the Roy O. Greep Laureate Award from the Endocrine Society, Leading Edge in Basic Science Award from the Society of Toxicology (SOT), and the Distinguished Scientist Award from the American College of Toxicology.

Dr. Walker studies genome: environment and epigenome: environment interactions to elucidate molecular mechanisms of disease. In addition to her own extramurally funded research program, Dr. Walker also directs the NIEHS T32 Training Program in Precision Environmental Health Sciences and is the Director of the NIEHS P30 Gulf Coast Center for Precision Environmental Health.

"EPIGENETIC AGING AS A TARGET FOR DEVELOPMENTAL REPROGRAMMING BY ENVIRONMENTAL EXPOSURES"

Longitudinal studies in mice exposed early in life to a diverse array of environmental exposures, revealed persistent reprogramming of the hepatic epigenome, and correlative changes in the transcriptome. Genes that undergo programmed aging (aging DEGs) comprised 40-60% of the exposure signatures of the xenoestrogen BPA, obesogen TBT, dioxin TCDD, and air pollutant PM2.5, with enhancers, and to a lesser extent, promoters, targeted for epigenomic reprogramming. H3K9me3 was relatively unchanged with age or exposure, H3K27me3 decreased with age but was unaffected by exposures, while H3K27ac, H3K4me1 and H3K4me3 were the primary marks that changed with age, and were targets for epigenomic reprogramming. Remarkably given their diverse mechanisms of action, BPA, TBT, TCDD and PM2.5 all induced a polarized attenuated aging signature in the liver with cell type- and directional-specificity. In parenchymal cells, expression of aging DEGs that would normally increase with age remained low, for example genes in Hepatocyte metabolic pathways. Conversely, in non-parenchymal cells, expression of aging DEGs in pathways that would normally decrease with age, such as ECM production by Stellate cells, remained high. This polarized attenuated aging signature correlated strongly with signatures obtained from cohorts of patients with liver disease and HCC and could distinguish healthy from diseased patient livers. Together, these studies reveal that the plasticity inherent in programmed epigenomic aging creates an early life vulnerability to reprogramming by a diverse range of environmental exposures, with consequences for the transcriptome, and disease risk, later in life.



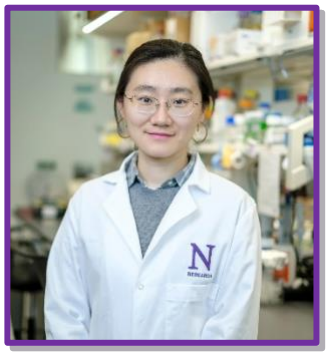
LU WANG, PH.D.

Assistant Professor, Biochemistry and Molecular Genetics
Northwestern University

Lu Wang is an Assistant Professor of Biochemistry and Molecular Genetics at Northwestern University. He obtained his Ph.D. from Nanjing University in China in 2011. He then completed his first postdoctoral training in cancer biology with Dr. Wei Xu at UW Madison, followed by a second postdoctoral training in cancer epigenetics with Dr. Ali Shilatifard. In 2019, he started his independent research career at Northwestern University. His lab focuses on understanding the genetic and epigenetic abnormalities involved in human diseases, identifying potential therapeutic targets, and developing novel therapies for treatment.

"MOLECULAR DISSECTION OF THE GENE ESSENTIALITY AND TRANSCRIPTIONAL REPROGRAMMING IN CANCER"

Small cell lung cancer (SCLC), which accounts for approximately 13% of all lung cancers, is recognized as a more aggressive form due to its rapid growth, early metastasis, and acquired resistance to therapy. Our previous studies identified and characterized a Polycomb-group protein, ASXL3, which is highly expressed in neuroendocrine SCLC cells. ASXL3 forms a multi-protein complex by linking the histone H2AK119 deubiquitinase BAP1 to the bromodomain protein BRD4 at active enhancer regions, thereby regulating enhancer activity and transcription in SCLC cells. Through unbiased genome-wide CRISPR screening and small molecule screening, we have identified the direct essential transcriptional targets of the BAP1/ASXL3/BRD4 axis and developed small molecule inhibitors targeting this oncogenic protein complex. Additionally, the oncogenic function of the ASXL3/BAP1 complex was further supported by our studies on the characterization of MBD6 protein as a key stabilizer of this complex in not only SCLC but also other cancer types. Recently, we have expanded our research to globally identify subtype-specific essential factors across different SCLC subtypes, aiming to understand their role in transcriptional reprogramming and to contribute to the development of personalized therapies for SCLC.



ZIBO ZHAO, PH.D.

Assistant Professor, Biochemistry and Molecular Genetics
Northwestern University

Dr. Zhao is an Assistant Professor in the Department of Biochemistry and Molecular Genetics at Northwestern University Feinberg School of Medicine. My research focuses on epigenetic regulation by the COMPASS (COMplex of Proteins ASociated with Set1) family of H3K4 methyltransferases and the roles of their mutations in human cancers and developmental diseases, with the development of novel therapeutics targeting synthetic lethality as an overarching goal. The evolutionarily conserved regulatory COMPASS complex plays a pivotal role in transcriptional activation by depositing methylation marks on histone 3 lysine 4 (H3K4me1/2/3) via the enzymatic activity of its methyltransferase subunit. In humans, the COMPASS family encompasses six methyltransferases, each of which forms a distinct complex with unique regulatory activity. In particular, MLL4/KMT2D and UTX/KDM6A within COMPASS are subject to high frequencies of recurrent somatic mutations in many cancers and in Kabuki Syndrome.

Our recent work depicted a targetable metabolic dependency arising from epigenetic factor deficiency, providing molecular insight to inform therapy for cancers with epigenetic alterations secondary to MLL4/UTX-COMPASS dysfunction. We also demonstrate that truncated cytoplasmic MLL4 predicts response to targeted metabolic inhibition therapy for bladder cancer and could be developed as a biomarker for KMT2D-mutated cancers. Our work highlights the broader potential for prognosis, patient stratification and treatment decision-making based on KMT2D mutation status in MLL4 truncation-relevant diseases, including human cancers and Kabuki Syndrome.

“MLL4/COMPASS DYSFUNCTION IN CANCER AND TREATMENT”

Epigenetic status–altering mutations in chromatin-modifying enzymes are a feature of human diseases, including many cancers. We investigated cellular dependencies, or vulnerabilities, which arise when enhancer function is compromised by loss of the frequently mutated COMPASS family members MLL3 and MLL4. Our CRISPR dropout screens revealed a targetable metabolic dependency arising from epigenetic factor deficiency, providing molecular insight to inform therapy for cancers with epigenetic alterations secondary to MLL3/4 COMPASS dysfunction. We also revealed strong evidence that there is an internal balance between promoter and enhancer usage dictated by MLL1 and MLL4 within COMPASS, and this equilibrium is subject to disruption during pathogenesis. Using a preclinical carcinogen model of bladder cancer in mouse, we demonstrate that truncated cytoplasmic MLL4 predicts response to targeted metabolic inhibition therapy for bladder cancer and could be developed as a biomarker for KMT2D-mutated cancers. We also highlight the broader potential for prognosis, patient stratification and treatment decision-making based on KMT2D mutation status in MLL4 truncation-relevant diseases, including human cancers and Kabuki Syndrome.

Due to the high prevalence of MLL4/KMT2D or UTX/KDM6A loss-of-function mutations in bladder cancer, we hypothesized that MLL4 mutation status may predict methotrexate responsiveness in bladder cancer treatment. Our study found that MLL4 mutant bladder cancer cells were selectively dependent on TYMS and showed heightened sensitivity to pemetrexed, a drug that inhibits TYMS, DHFR, and GART. This suggests that targeting multiple enzymes within the one-carbon metabolism could be a promising approach for treating MLL4/UTX-COMPASS mutant bladder cancer. Based on our previous and current findings, a clinical trial using pemetrexed in MLL4/UTX-COMPASS mutant solid tumors is being launched at Northwestern Medicine.

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SQE Symposium Committee
Dr. Lu Wang and Dr. Andrea Piunti
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