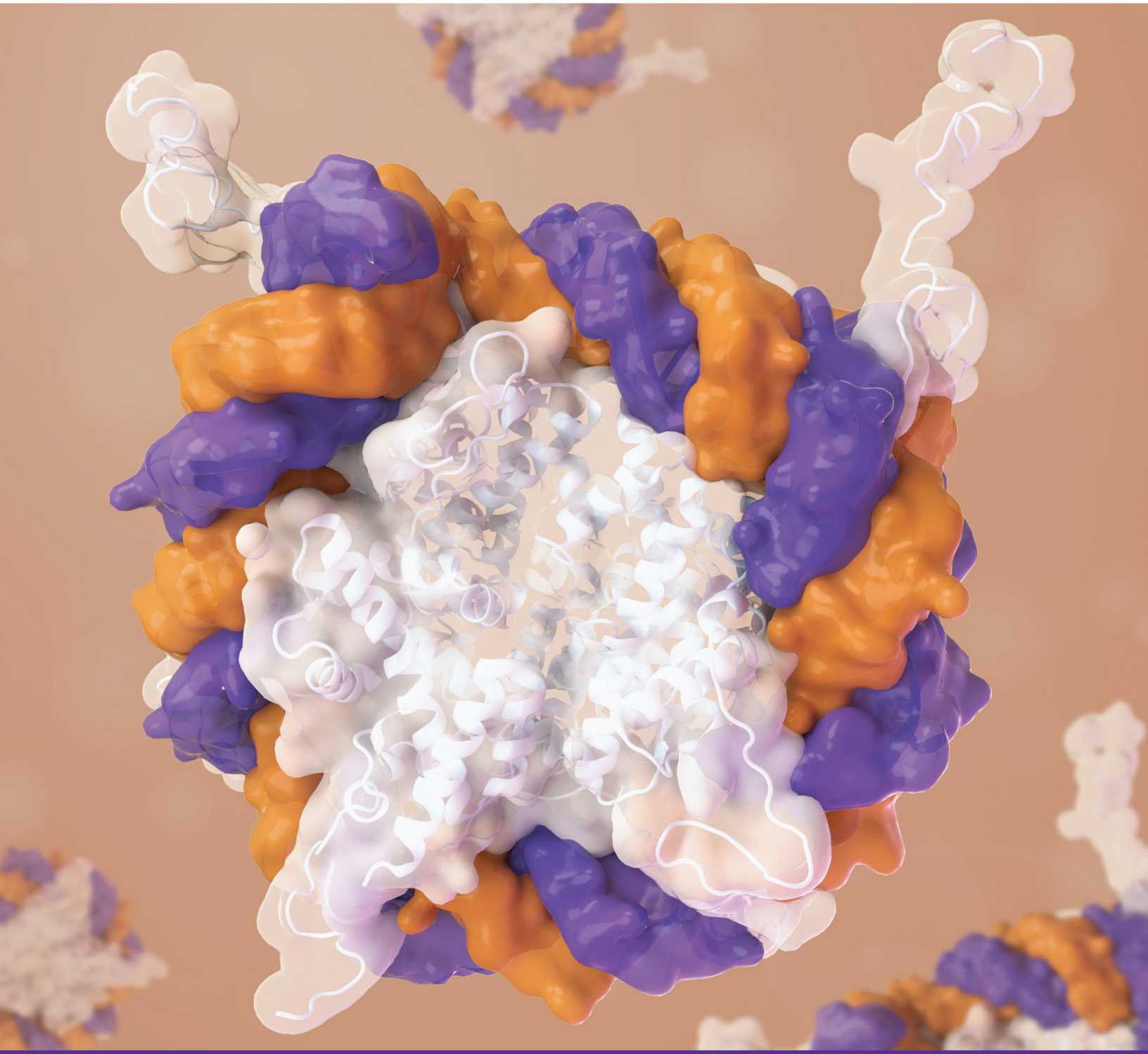
NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR GENETICS



NINTH ANNUAL RETREAT
SEPTEMBER 18, 2025

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ITINERARY

SIMPSON QUERREY BIOMEDICAL RESEARCH CENTER POTOCSNAK ATRIUM

8:30 - 9:00am Breakfast and Poster Setup

10:30 - 12:00pm Poster Session

12:00 - 1:00pm Lunch

SIMPSON QUERREY BIOMEDICAL RESEARCH CENTER AUDITORIUM

9:00 - 9:10 AM Ali Shilatifard, PhD, Chairman, Biochemistry and Molecular Genetics, Simpson Querrey Institute for Epigenetics
Department Overview and Welcoming Remarks

9:10 - 10:30 AM Lab Recaps

1:00 PM *Meet at SQE Atrium to walk over to law school*

NORTHWESTERN UNIVERSITY PRITZKER SCHOOL OF LAW LINCOLN HALL

1:15 - 1:30 PM Introduction of Keynote Speaker

1:30 - 2:15 PM Keynote Speaker: Ronald A. DePinho, MD
Harry Graves Burkhart III Distinguished University Chair
Professor, Department of Cancer Biology
Past President of UT MD Anderson Cancer Center
"Telomerase in Cancer and Aging"

2:15 - 2:30 PM Q&A

2:30 - 2:55 PM Short Talk: Saeid Parast, PhD, NRSA Postdoctoral Fellow, Shilatifard Laboratory
"ELOA-Mediated Integration of Transcription Elongation and mRNA 3' End Processing in Cellular Senescence Programs"

2:55 - 3:20 PM Short Talk: Mushtaq Nengroo, PhD, Postdoctoral Fellow, Ben-Sahra and Mendillo Laboratories
"Accumulation of succinate suppresses de novo purine synthesis through succinylation-mediated control of the mitochondrial folate cycle"

3:20 - 3:45 PM Short Talk: Shashank Srivastava, PhD, Research Assistant Professor, Foltz Laboratory
"Nucleotide Metabolism-Chromatin Assembly Nexus: Unraveling the Cooperative Regulatory Mechanisms"

3:45 - 4:00 PM Conclusion and Awards

NORTHWESTERN UNIVERSITY PRITZKER SCHOOL OF LAW THE JUSTICE JOHN PAUL STEVENS COURTYARD

4:00 - 6:00 PM Reception

KEYNOTE SPEAKER

Ronald A. DePinho, MD, PhD(hc), DSc(hc)

Harry Graves Burkhart III
Distinguished University Chair,
Professor, Department of Cancer Biology,
Past President, UT MD Anderson Cancer Center

Ronald A. DePinho, M.D. is past president and professor of UT MD Anderson Cancer Center. Dr. DePinho received his M.D. degree from Albert Einstein College of Medicine, conducted residency and postdoctoral training at Columbia, and served as faculty at Einstein, DFCI/Harvard and MD Anderson. At MD Anderson, he launched the Moon Shots Program, inspiring the Biden national cancer moonshot. His laboratory elucidated the core molecular pathway for aging, link between advancing age and increased cancer incidence, and reversibility of aging He founded several biotechnology companies. His honors include Szent-Györgyi Prize, AACR Clowes Award, Ellis Island Medal of Honor, Portuguese knighthood, and honorary degrees. He is a member of the National Academies of Science and Medicine and a fellow of the American Academy of Arts and Sciences, AAAS and AACR.

Telomerase in Cancer and Aging

The escalating social and economic burden of an aging global population has placed aging research at the forefront of biomedical science. Aging is the greatest risk factor for chronic diseases such as cancer, cardiovascular disease (CVD), and Alzheimer's disease (AD). How aging mechanisms intersect with those driving these conditions remains an active area of investigation. The hallmarks of aging encompass a diverse array of molecular mechanisms and cellular systems that interrelate and collectively propel the aging process. Through the lens of telomere biology, we have explored how telomerase and telomere dysfunction amplify these underlying processes and contribute to age-related diseases.

Our research demonstrates that insufficient telomerase activity—primarily due to low transcription of the telomerase reverse transcriptase (TERT) gene—leads to telomere dysfunction and subsequent aging pathologies, including cancer. Utilizing an inducible TERT-ER model, we showed that aging is a reversible process. Beyond its classical role in telomere synthesis, TERT functions as a transcriptional co-regulator of genes critical to aging and associated diseases. Notably, the TERT gene is epigenetically repressed in all somatic cells at the onset of aging in both mice and humans.

To explore whether restoring TERT activity could alter the course of aging, we conducted a series of genetic and pharmacological studies. In addition to TERT transgenic approaches to maintain TERT expression, high-throughput screening (HTS) was used to identify TERT activator compounds (TAC) capable of de-repressing the TERT locus. In primary human cells and naturally aged mice, TAC-induced elevation of TERT levels promoted telomere synthesis, attenuated key tissue aging hallmarks—including reduced cellular senescence and inflammatory cytokine production—and silenced p16^INK4a expression via upregulation of DNMT3B-mediated promoter hypermethylation. In the brain, TAC alleviated neuroinflammation, increased neurotrophic factors, stimulated adult neurogenesis, and preserved cognitive function without apparent toxicity or increased cancer risk.

Collectively, these findings underscore TERT's critical role in aging and provide preclinical proof-of-concept for physiological TERT activation as a strategy to mitigate multiple aging hallmarks and their associated pathologies.

Saeid Parast, PhD

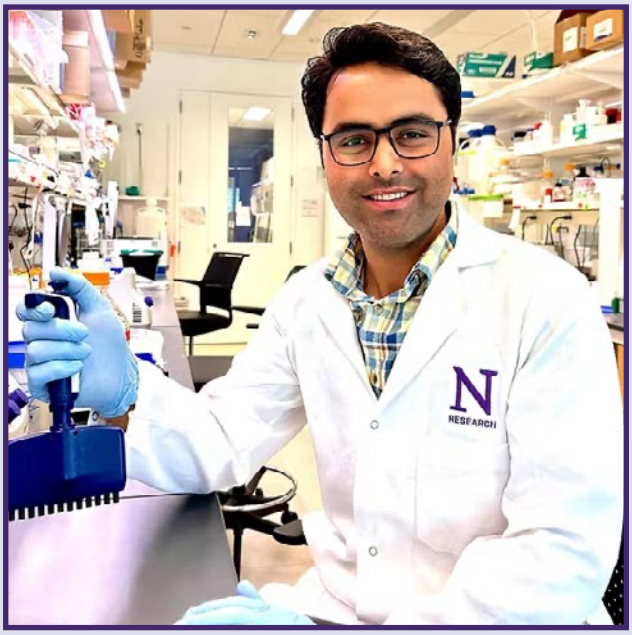
NRSA Postdoctoral Fellow,
Shilatifard Laboratory

"ELOA-Mediated Integration of Transcription Elongation and mRNA 3' End Processing in Cellular Senescence Programs"

Mushtaq Nengroo, PhD

Postdoctoral Fellow, Ben-Sahra and Mendillo Laboratories

"Accumulation of succinate suppresses de novo purine synthesis through succinylation-mediated control of the mitochondrial folate cycle"



Shashank Srivastava, PhD

Research Assistant Professor
Foltz Laboratory

"Nucleotide Metabolism-Chromatin Assembly Nexus: Unraveling the Cooperative Regulatory Mechanisms"

POSTER SUBMISSIONS

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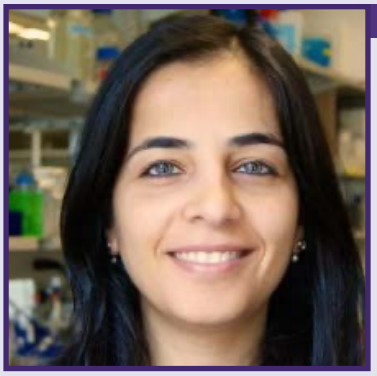
Koke Abe, PhD

Postdoctoral Fellow, Lauberth Lab, Biochemistry and Molecular Genetics, Northwestern University

Kouki Abe, Mannan Bohla, Andrew Loiacono, Ria Amesur, Bei Liu, Ava Maurine Neuman, Lauren Mi-Young Weil, Dan Foltz, Chuan He, Sui Huang, Shannon M. Lauberth

RNA-Binding Function of TOP1 Coordinates Ribosome Biogenesis in Colon Cancer

Ribosome biogenesis is a central biosynthetic pathway hijacked by cancer cells to support uncontrolled growth, rendering the nucleolus a therapeutic vulnerability. We discovered that Topoisomerase I (TOP1) directly binds pre-rRNAs and box C/D snoRNAs through a defined RNA-binding region, anchoring it to U3 snoRNP proteins in the nucleolus. This RNA-dependent function of TOP1 coordinates rRNA transcription and co-transcriptional processing. Genetic disruption of TOP1-RNA binding induces Pol I stalling, failure of snoRNA-guided rRNA maturation, and nucleolar disorganization. We further identify a selective small-molecule inhibitor that disrupts TOP1-RNA interactions without affecting its DNA-relaxation activity, phenocopying the genetic disruption and suppressing tumor cell proliferation. These findings establish a new RNA-binding role for TOP1 in nucleolar homeostasis and suggest a therapeutic strategy to target ribosome biogenesis in colorectal cancer.



Milad Alasady, PhD

Research Associate, Mendillo Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Milad J. Alasady, Austin T. Klein, and Marc L. Mendillo

Identifying key regulators of stress response pathways

Heat Shock Factor 1 (HSF1) is a key regulator of the heat-shock response (HSR) and crucial for protein homeostasis. In cancer, HSF1 drives a transcriptional program that includes not only canonical heat shock proteins (HSPs) involved in proteostasis, but also non-canonical genes linked to processes such as proliferation, metabolism, and cellular adhesion. We recently identified one such non-canonical target, JMJD6, as an essential mediator of HSF1 activity through a genome-wide RNAi screen. JMJD6 enhances HSF1 activation by disrupting repressive HSP70-HSF1 complexes. In a positive feedback loop, HSF1 binds to and promotes JMJD6 expression, which reduces HSP70 R469 monomethylation, further disrupting HSP70-HSF1 complexes and enhancing HSF1 activation. Together, these findings underscore the importance of methylation dynamics and stress-response pathways in regulating protein homeostasis. Building on these findings, we are currently mapping HSF1 protein interactions with targeted modulation of the proteostasis network. This combined approach will allow for the identification of critical regulators that control stress adaptation, with the potential to uncover novel therapeutic targets in cancer and other proteotoxic conditions.

Claire Chaikin

PhD Candidate, Peek Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Claire Chaikin, Abishek Vijay Thakkar, Adam Wei Tsun Steffeck, Eric Pfrender, Pei Zhu, Issam Ben-Sahra, Clara Peek

Circadian clock-HIF regulation of muscle metabolism and mass maintenance during diet-induced obesity

Epidemiological and genetic studies show that circadian rhythm disruption leads to accelerated and worsened symptoms of metabolic syndrome. Studies indicate that core clock factor, BMAL1, is required for skeletal muscle glucose uptake in lean mice; however, the clock's role in skeletal muscle metabolism during metabolic stress is unclear. Recent work uncovered a link between the molecular clock and hypoxia inducible factor (HIF) response pathway, which is known to control the induction of glycolytic metabolism in skeletal muscle during nutrient stress. We hypothesize that the skeletal muscle clock mediates glucose utilization and downstream muscle metabolism during diet-induced obesity (DIO) through HIF activity regulation. We generated muscle-specific BMAL1-deficient mice and muscle-specific BMAL1-deficient, HIF1α stabilized mice to investigate BMAL1-HIF interactions. During DIO, muscle BMAL1-deficient mice display reduced HIF1α target gene expression and impaired glucose tolerance. Furthermore, 13C6-glucose tracing and RNA-sequencing studies revealed reduced levels of key glycolytic intermediates and enzymes in BMAL1-deficient muscle. We found that HIF1α stabilization in muscle BMAL1-deficient mice rescues glucose tolerance and 30% of downregulated genes from muscle BMAL1-deficient mice. Additionally, we observed that muscle BMAL1-deficient mice have reduced muscle mass and cross-sectional area, along with elevated levels of free amino acids, suggesting impaired muscle protein homeostasis. Interestingly, autophagic flux was elevated in BMAL1-deficient muscle and more intriguingly, protein synthesis rates were also elevated, potentially suggesting increased protein turnover. Overall, these data provide evidence of an interaction between the molecular clock and HIF response pathways that impacts whole-body glucose disposal and skeletal muscle transcriptional and metabolic adaptations during DIO.

Evan Couser

PhD Candidate, Eichner Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Evan Couser, Austin T. Klein, Bryce A. Van Bree, Marc L. Mendillo, Lillian J. Eichner

Determining LKB1-specific mechanisms of therapeutic resistance in NSCLC

LKB1/Stk11 mutant Non-Small Cell Lung Cancer (NSCLC) is a distinct subtype of NSCLC characterized by poor patient outcome and therapeutic resistance to standard-of-care therapies. Previous work from the Eichner lab uncovered an LKB1-specific mechanism of therapeutic resistance. Here, we use CRISPR screening to explore the concept of LKB1-specific therapeutic mechanisms genome-wide. Findings confirm that LKB1 status alters the therapeutic resistance mechanisms employed by lung cancer cells. The implication is that it is necessary to identify LKB1-specific mechanisms of therapeutic resistance to overcome therapeutic resistance in LKB1 mutant lung cancer cells. Therefore, we validated the top LKB1-specific dependency identified by CRISPR screens in vitro and in vivo. Integration of transcriptional profiling with results from CRISPR screens revealed that regulation of an epigenetic factor ensures tumor cell survival during drug resistance. Ongoing experiments are aimed at defining how the LKB1 kinase pathway intersects with this novel dependency in therapeutic resistance.

Yue He

PhD Candidate, Shilatifard Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Yue He, Saeid Mohammad Parast, Jacob Martin Zeidner
Sarah Gold, Ali Shilatifard

Characterization of a novel function for ELOA as an elongation factor regulating cellular senescence

Cellular senescence is a typically irreversible process characterized by cell cycle arrest, morphological changes, and secretion of inflammatory factors. Physiologically, cellular senescence contributes to tissue dysfunction, neoplastic transformation, and age-related diseases. Many transcription factors related to RNA Polymerase II (RNAPII) have been reported to be involved in the induction of cellular senescence. However, the underlying mechanisms (and potential targets for therapeutic interventions) remain largely elusive. Here, by combining next-generation sequencing and biochemical assays, we demonstrate that depletion of the transcription factor SPT6 promotes cellular senescence-associated gene expression phenotypes, including suspended proliferation and robustly detectable β-galactosidase activity. Through a genome-wide CRISPR screen, we identified the transcriptional elongation factor ELOA as a regulator of cellular senescence. Interestingly, loss of ELOA rescued the proliferation defect caused by SPT6 depletion. ELOA knockout also led to downregulation of the senescence entry marker p21, suggesting a direct role for ELOA in the transcriptional regulation of cellular senescence. Overall, our results shed light on ELOA as a potential therapeutic target in future approaches to limit or reverse cellular senescence.

Evra Ho

Research Technician, Mendillo Lab, Biochemistry and Molecular Genetics, Northwestern University

Sammy Alhayek, **Tai-Yuan Ho**, Austin Klein, Manisha Joseph, David R. Amici, Josiah Wong, Jasen M Jackson, Sara Fernandez Dunne, Elizabeth T. Bartom, Dai Horiuchi, Marc L. Mendillo

High-throughput chemical-genetic mapping to identify compound mechanisms, and mediators of drug sensitivity and resistance

Large-scale tumor sequencing has revealed extensive catalogs of cancer-specific genetic alterations, yet the functional consequences of most remain unknown. We applied QMAP-Seq, a high-throughput chemical–genetic profiling platform, to systematically define how common alterations in genome maintenance pathways influence drug response. A CRISPR library targeting 62 genes frequently altered in invasive breast carcinoma was profiled against 760 compounds spanning DNA damage, cell cycle, protein homeostasis, and epigenetic pathways. The resulting >45,000 chemical–genetic interactions uncovered 84 strong therapeutic and 39 resistance interactions. These included clinically validated or clinically tested strategies across multiple categories: targeted therapies such as PARP inhibition for BRCA1 mutations, resistance mechanisms such as RB1 loss conferring CDK4/6 inhibitor resistance, and combination approaches such as cisplatin with ATR inhibition. We also identified novel therapeutic candidates, off-target effects, and divergent sensitivity profiles among compounds with shared mechanisms, underscoring the influence of chemical structure on biological activity. Together, these findings demonstrate the power of QMAP-Seq to connect genomic alterations with drug response, enabling discovery of clinically actionable vulnerabilities and resistance mechanisms.

Marta Iwanaszko, PhD

Research Assistant Professor, Shilatifard Lab, Biochemistry and Molecular Genetics, Northwestern University

Saeid M Parast, Madhurima Das, Simai Wang, Vijay Ramani, **Marta Iwanaszko**, Ali Shilatifard

The long and short of it: age-dependent changes in RNAPII-mediated transcription of genes with different length

Aging involves a gradual decline in molecular, cellular, and physiological functions, leading to diminished vitality and the onset of age-related diseases. Despite advances in omics technologies, the functional status of basal transcription processes in aging remains insufficiently understood. To address this, we conducted a comprehensive transcriptomic analysis of the brains and other tissues of young (3 months) and old (24 months) mice using bulk short read and long-read RNA sequencing.

We developed a novel algorithm capable of distinguishing old tissues from young based on intronic coverage in large and extra-large exons. Contrary to recently reported changes in the slope of the intronic coverage, indicating difference in the speed of elongation, we did not observe that phenomenon but rather a stable change in the amplitude of coverage over large and extra-large introns, which globally decreased with aging especially in tissues with low regenerative ability, like brain.

Our analysis revealed that the aged brain exhibited an enriched representation of genes connected to phagosome and microglia phagocytosis, synapse pruning, immune response, and neutrophil activation. In contrast, downregulated genes in the aged brain were associated with processes such as nervous system development, neuron projection, synapse organization, and gliogenesis. We validated these findings using published human RNA-seq data and observed similar characteristics in the aging human brain, corroborating our mouse model results. Furthermore, significant changes were noted in the spliceosome during aging, correlating with short-read RNA-seq data and showing significant downregulation of genes and isoforms in the aged brain. Additionally, the aged brain showed significant overrepresentation of mono-exonic isoforms and novel intron retention isoforms. Our biochemical studies showed a significant decrease in the association of Med23, a mediator complex subunit, with RNAPII in aged mice, suggesting an altered transcriptional machinery.

Our findings underscore the importance of studying mRNA splicing events and transcriptional dynamics in the context of aging and provide a robust framework for identifying age-related transcriptomic changes. The observed reduction in mRNA dynamics and the altered regulatory role of RNA-binding proteins in the aged brain suggest a reshaping of the transcriptome with aging, driven by changes in splicing and mRNA processing.

Bridget Lear, PhD

Research Associate Professor,
Shilatifard Lab, Biochemistry and Molecular Genetics, Northwestern University

Bridget C. Lear, Mandy Bu, Hamza Hasan, and Ali Shilatifard

A synthetic lethality screen in Drosophila to identify molecular pathways impacted by loss of H3K4 monomethylation

Histone H3K4 monomethylation (H3K4me1) at active enhancers is highly conserved in eukaryotes, mediated by COMPASS-like methyltransferase family members including MLL3/MLL4 in mammals and Trithorax-like (TRR) in Drosophila. Despite broad conservation, loss of H3K4me1 at enhancers through mutation of MLL3/MLL4 or TRR catalytic domains has minimal effects on gene expression. Furthermore, whereas complete loss of TRR function in Drosophila results in developmental lethality, mutants that lack TRR methyltransferase activity are viable and exhibit few detectable phenotypes. To identify novel mechanisms by which H3K4me1 impacts gene expression and development, we have established a screening approach in Drosophila to identify genes that are essential for development specifically in H3K4me1-deficient animals. In this screen we combine a catalytically-deficient allele of trr (trrCA) with RNAi knockdown of genes of interest. In the initial screen we are targeting approximately 2000 transcription-related genes using a library of ~2500 transgenic Drosophila RNAi strains. Of the first ~585 strains screened, we have identified 35 primary 'hits' that exhibit developmental lethality when RNAi knockdown is combined with trrCA. Secondary screening of primary hits includes replication of the initial finding and confirmation that the lethality phenotype is specific to catalytically-deficient trr variants. Thus far, our secondary screening results indicate a replication/specificity rate of roughly 30%. Among the initial replicated hits is the known COMPASS-like subunit UTX, which demonstrates that the screening strategy can detect genes with functional significance to TRR. Replicated hits will be subject to additional experiments including validation with independent RNAi reagents, evaluation of tissue-specific phenotypic interactions, and assessment of changes in gene expression. Hits of interest will also be evaluated in mammalian cells to assess conservation of phenotypic and molecular interactions.

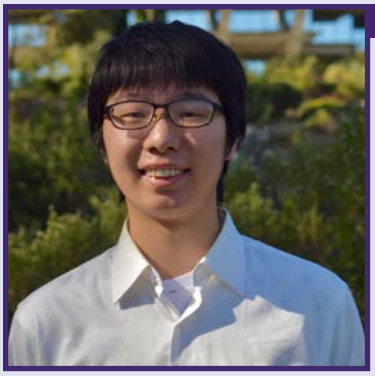
Amanda Luvisotto

PhD Candidate, Wang Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Amanda Luvisotto, Oguzhan Beytullahoglu, Rima Tulaiha, Lu Wang

Molecular Dissection of Gene Essentiality in Small Cell Lung Cancer

Small Cell Lung Cancer (SCLC) is primarily divided into four main subtypes based on the expression of lineage-specific transcription factors: SCLC-A, SCLC-N, SCLC-P, and SCLC-Y. Molecular profiling of SCLC has revealed that each subtype is transcriptionally distinct, with unique biomarkers and dependencies, suggesting that each variant may rely on unique signaling pathways underlying their survival and proliferation. Previously, our lab identified over 300 subtype-specific essential factors in SCLC cell lines. Among these, the TOX high mobility group box family member 3 (TOX3) emerged as a top essential transcription factor in SCLC-A. While TOX3 has established roles in neural progenitor identity and neuronal survival, its function in SCLC remains largely unexplored. To investigate this, we depleted TOX3 in multiple SCLC cell lines, which led to a marked reduction in cell growth, and we profiled gene expression changes associated with its loss. In addition, we successfully generated a ChIP-grade antibody against TOX3 and, for the first time, characterized TOX3 occupancy at the chromatin level. Our findings reveal that TOX3 binds to both active and inactive chromatin loci, with MYCL emerging as a major transcriptional target of TOX3 in multiple SCLC-A cell lines. Together, these results position TOX3 as a critical transcriptional regulator of SCLC-A and highlight its potential as a therapeutic vulnerability.



Jiayan Ma

PhD Candidate, Liu Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Hailu Fu, **Jiayan Ma**, Eric Tong, Mark Youngblood, Feng Yue, Li Wang, Yaping Liu

snNOMeHiC: joint profiling of 3D genome, DNA methylation, and chromatin accessibility from the same nuclei at flash-frozen tissue and primary tumor sample

Epigenetic marks, including DNA methylation, chromatin accessibility, and three-dimensional (3D) genome organization, play instrumental roles in gene regulation in mammals. Gene activation or repression potential, however, cannot be entirely predicted by looking at a single modality. Accurate predictive models require multiple modalities simultaneously. We previously developed single-cell Methyl-HiC technology to jointly profile DNA methylation and 3D genome from the same cells. Further, we incorporated an additional footprint of GpC methyltransferase activity (i.e., chromatin accessibility) into the assay, named NOMe-HiC, but at the bulk level.

Here, we extended NOMe-HiC technology to the single-cell level to enable the joint profiling of the 3D genome, DNA methylation, and chromatin accessibility from the same nuclei. We performed snNOMe-HiC at IMR-90 cell lines and found high concordance across all three modalities with the bulk NOMe-HiC by pooling the single cells. We further prepared a mixture of GM12878 and IMR-90 cells and processed the cell mixture with snNOMe-HiC. snNOMe-HiC can distinguish the two cell types using each of the three epigenetic features, respectively. To benchmark the performance of snNOMe-HiC at flash-frozen heterogeneous tissues, we generated snNOMe-HiC data from ~2000 nuclei at flash-frozen mice cortex. We identified all the major known cell types in the previous studies across three modalities and showed reproducible results across replicates. Finally, we applied snNOMe-HiC to a primary meningioma sample. We identified previously known copy number alterations in tumor-related cell clusters and found concordant changes of epigenetic heterogeneity across cell populations, which can potentially reveal the crosstalk between genetics and multiple epigenetic marks during the clonal evolution in cancer progression. In summary, snNOMe-HiC is a robust technology that can profile three epigenetic modalities and genetic aberrations in the same nuclei from flash-frozen tissues and primary tumors.

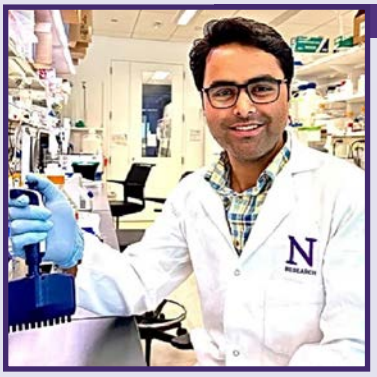
Allegra Minor

PhD Candidate, Eichner Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Allegra C. Minor, Irena Gushterova, Bryce Van Bree, Lillian J. Eichner

Self-Restraint: Senescence induction in KRAS, LKB1 mutant lung cancer

Non-Small Cell Lung Cancer (NSCLC) is one of the leading causes of cancer-related death in the U.S., and coincident mutation in the oncogene KRAS and the tumor suppressor LKB1/STK11 (KL) defines a major subtype of NSCLC. KL lung tumors are characterized by aggressive growth and poor patient outcomes, in part due to resistance to standard-of-care treatments. One avenue of tumor control which has yet to be explored to its full potential is the induction of senescence and manipulation of the accompanying Senescence-Associated Secretory Phenotype (SASP). Based on findings from the Eichner Lab, we hypothesize that endogenous regulators are actively restraining senescence in KL tumors, and that identifying these regulators could yield opportunities for therapeutically exploiting the senescence program. Here, we show that genetic, biochemical, and physical perturbation can each be used to induce KL lung tumor cells to undergo senescence. Using genetically engineered mouse models and single cell RNA-sequencing, we have identified populations of senescent-like cells in vivo and ex vivo. Ongoing work is defining mechanism of senescence restraint in KL NSCLC.



Mushtaq Nengroo, PhD

Postdoctoral Fellow, Ben-Sahra & Mendillo Labs, Biochemistry and Molecular Genetics, Northwestern University

Mushtaq A. Nengroo, Austin T. Klein, Heather S. Carr, Olivia Vidal-Cruchez, Umakant Sahu, Daniel J. McGrail, Nidhi Sahni, Peter A. Faull, Peng Gao, John M. Asara, Hardik Shah, Marc L. Mendillo, Issam Ben-Sahra

Accumulation of succinate suppresses de novo purine synthesis through succinylation-mediated control of the mitochondrial folate cycle

The de novo purine synthesis pathway is essential for nucleic acid production and cellular energy, but the role of mitochondrial metabolism in regulating this process remains underexplored. In cancer, metabolic reprogramming supports rapid growth, yet the specific roles of tricarboxylic acid (TCA) cycle enzymes in nucleotide biosynthesis are not fully understood. Here, we show that the TCA cycle enzyme succinate dehydrogenase (SDH) is vital for maintaining optimal de novo purine synthesis in both normal and cancer cells. Genetic or drug-based inhibition of SDH significantly reduces purine synthesis, leading to a notable decline in cell proliferation. Mechanistically, SDH inhibition causes succinate buildup, which promotes the succinylation of serine hydroxymethyltransferase 2 (SHMT2), a key enzyme within the mitochondrial tetrahydrofolate (THF) cycle, thereby decreasing cellular formate production and limiting the one-carbon units needed for purine synthesis. In response, cancer cells compensate by increasing the purine salvage pathway, a metabolic adaptation that could serve as a therapeutic vulnerability. Notably, the combined inhibition of SDH and the purine salvage pathway produces strong antiproliferative and antitumor effects in preclinical models. These findings not only reveal a signaling role for mitochondrial succinate in controlling purine metabolism but also suggest a promising therapeutic approach for targeting metabolic dependencies in cancer.

Mark Youngblood, MD, PhD

Resident in Neurological Surgery,
Post-Doctoral Researcher, Yue Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Juan Wan, PhD

Post-Doctoral Scholar, Yue Lab,
Biochemistry and Molecular Genetics,
Northwestern University

Mark Youngblood, **Juan Wang**, Qixuan Wang, Lena Ann Stasiak, Mateo Gomez, Yihao Fu, Ping Wang, Josiah Wong, Harrshavasan Congivaram, Pouya Jamshidi, Madina Sukhanova, Kathleen McCortney, Matthew Tate, Adam M Sonabend, Maciej Lesniak, James Chandler, Amy Heimberger, David Raleigh, Stephen Magill, Craig Horbinski, Feng Yue

Epigenetic architecture of Meningioma subgroups reveals prognostic molecular drivers and new translational targets

Recent transcriptional and DNA methylation studies have led to clinically practical classification schemes for meningiomas, however the biological significance and routes underlying formation of these subgroups are poorly understood. In this study, we performed comprehensive and integrated molecular characterization of meningiomas, aiming to unravel downstream oncogenic mechanisms to direct future translational efforts. Freshly resected meningioma tissues were profiled to capture gene expression patterns (RNA-seq; n = 124), genome-wide DNA methylation (WGBS; n = 28), chromatin topology (Hi-C; n = 42), and DNA markers (ChIP-seq for H3K27ac, H3K27me3, CTCF; n = 6 each), across a group of molecularly and prognostically diverse tumors. We identified key structural variants that drive meningioma biology, mediated through epigenetic remodeling and transcriptional hijacking events that re-wire chromatin architecture. A subset of meningiomas exhibit focal amplifications that result in marked changes in oncogene expression, including formation of ecDNA species. We identified thousands of subtype specific A/B compartments, differentially methylated regions and chromatin loops. Association of DNA methylation patterns with CTCF binding and loop formation regulates subgroup-specific gene expression patterns and topology domains, ultimately resulting in varying levels of clinical aggressiveness. Our work provides an epigenetic foundation to understand prognostic subgroups of meningiomas, and identifies new molecular targets to improve management of these common brain tumors.

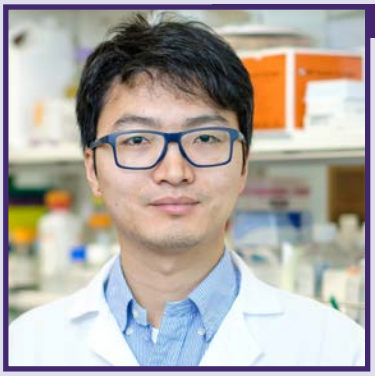
Jacob Zeidner

Research Technician, Shilatifard Lab, Biochemistry and Molecular Genetics, Northwestern University

Saeid Parast, Simai Wang, Marta Iwanaszko, Yue He, Deniz G Olgun, Sarah R Gold, Yuki Aoi, **Jacob M Zeidner**, Benjamin C Howard, William R Thakur, Vijay Ramani, Ali Shilatifard

Transcriptional Elongation Crisis/3'-End Processing Control by ELOA in Reversible Growth Arrest

Transcription elongation factors control post-initiation steps of gene expression by RNA polymerase II (RNAPII). We have established distinct mechanistic roles for the essential elongation factors PAF1, NELF, SPT5, SPT6, and the Super Elongation Complex (SEC) via acute depletion of each individually in auxin-inducible degron lines. Here, we leverage these degron lines to explore the regulatory intersection of transcription elongation control and pre-mRNA processing. Integrating long- and short-read RNA-seq data to quantify transcript isoform usage at single-molecule resolution, we identify elongation factor-specific RNA processing regulons including a cellular senescence-enriched regulon shared by NELF and SPT6. We then show that long-term depletion of NELF or SPT6 results in reversible growth arrest following early upregulation of a small group of genes, which include the senescence-associated genes CDKN1A (p21) and CCN2. We perform genetic suppressor screens that implicate the elongation factor Elongin A (ELOA) in NELF or SPT6 depletion-induced growth arrest. ELOA loss suppresses NELF depletion-induced pre-mRNA processing defects and the 3' extension of RNAPII occupancy past transcription end sites (TES) at genes induced by NELF depletion. ELOA also occupies TES-proximal regions under normal conditions, and acute ELOA depletion results in a loss of RNAPII processivity at the 3' end of genes, opposing the effects of NELF or SPT6 depletion. Finally, we demonstrate that genetic loss of ELOA confers a growth advantage to aging human primary dermal fibroblasts. These findings establish the existence of novel ELOA-dependent mechanisms regulating transcription maturation, and links these mechanisms to the complex phenomena of cellular senescence and aging.



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BRD2 bridges TFIID and histone acetylation to promote transcriptional initiation

Members of the bromodomain and extraterminal domain (BET) protein family play a central role in transcription by RNA Polymerase II (Pol II). Small-molecule inhibitors that block interaction between BET bromodomains and acetylated histones have been developed to achieve therapeutic benefit. However, the BET protein BRD4 does not require bromodomains to perform its major transcriptional elongation function, and the mechanisms by which other BET proteins regulate transcription remain incompletely understood. Addressing the disparity between pan-BET degraders and BRD4-specific depletion, we report that the BET protein BRD2 generally functions to promote transcriptional initiation in a bromodomain-dependent manner at both promoters and enhancers in human cells. We demonstrate that BRD2 bromodomains preferentially bind to tetra-acetylated histones harboring MOF-mediated H4K16ac, while the BRD2 C terminal domain facilitates recruitment of TFIID. Our studies provide mechanistic insight into the distinct roles of BRD2 in transcriptional initiation through the recruitment of TFIID and BRD4 in transcriptional elongation through the recruitment of CDK9 and controlling proper regulation of gene expression.

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Immunomodulatory role of the stem cell circadian clock in muscle repair

Circadian rhythms orchestrate physiological processes such as metabolism, immune function, and tissue regeneration, aligning them with the optimal time of day (TOD). This study identifies an interplay between the circadian clock within muscle stem cells (SCs) and their capacity to modulate the immune microenvironment during muscle regeneration. We reveal that the SC clock triggers TOD–dependent inflammatory gene transcription after injury, particularly genes related to neutrophil activity and chemotaxis. These responses are driven by cytosolic regeneration of the signaling metabolite nicotinamide adenine dinucleotide (oxidized form) (NAD+), as enhancing cytosolic NAD+ regeneration in SCs is sufficient to induce inflammatory responses that influence muscle regeneration. Mononuclear single-cell sequencing of the regenerating muscle niche further implicates the cytokine CCL2 in mediating SC-neutrophil cross-talk in a TOD-dependent manner. Our findings highlight the intersection between SC metabolic shifts and immune responses within the muscle microenvironment, dictated by circadian rhythms, and underscore the potential for targeting circadian and metabolic pathways to enhance tissue regeneration.

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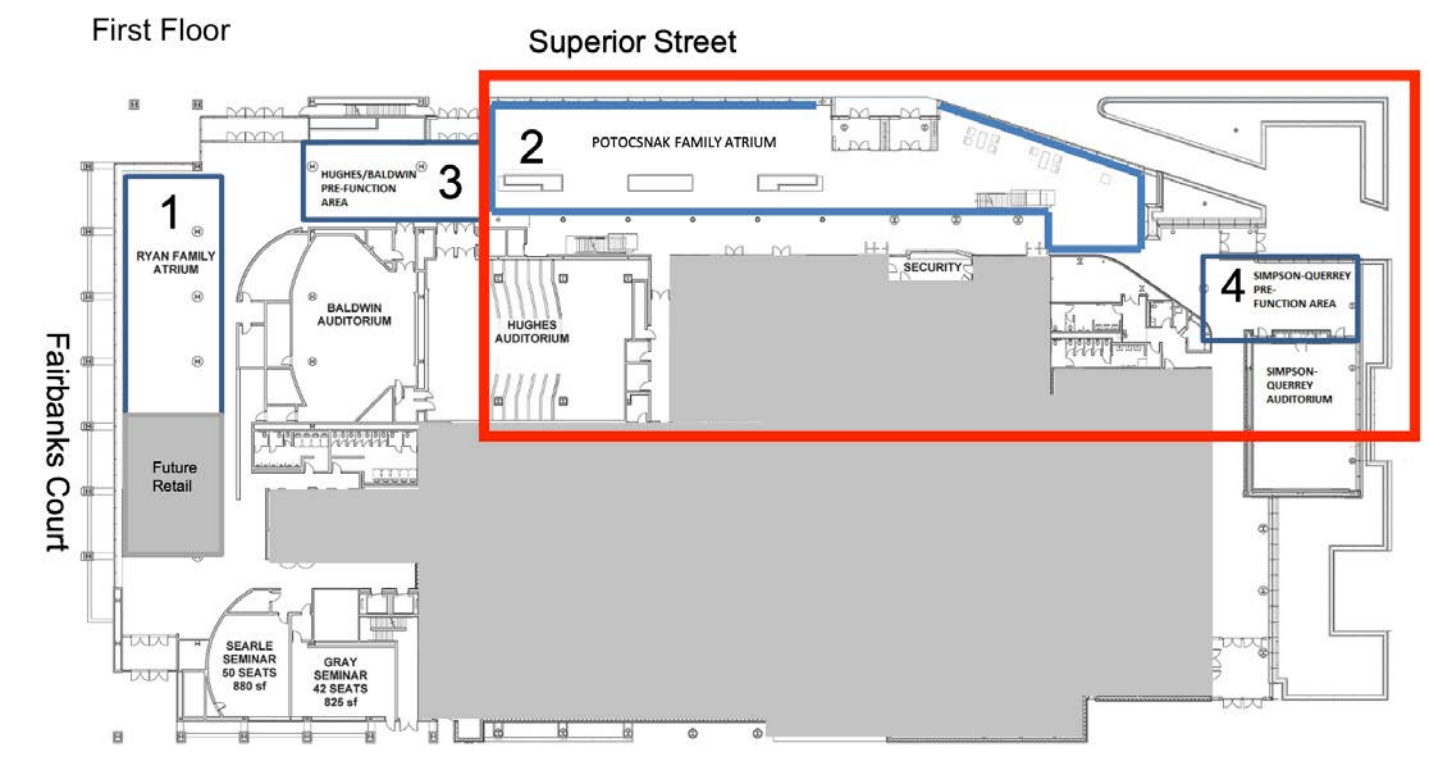

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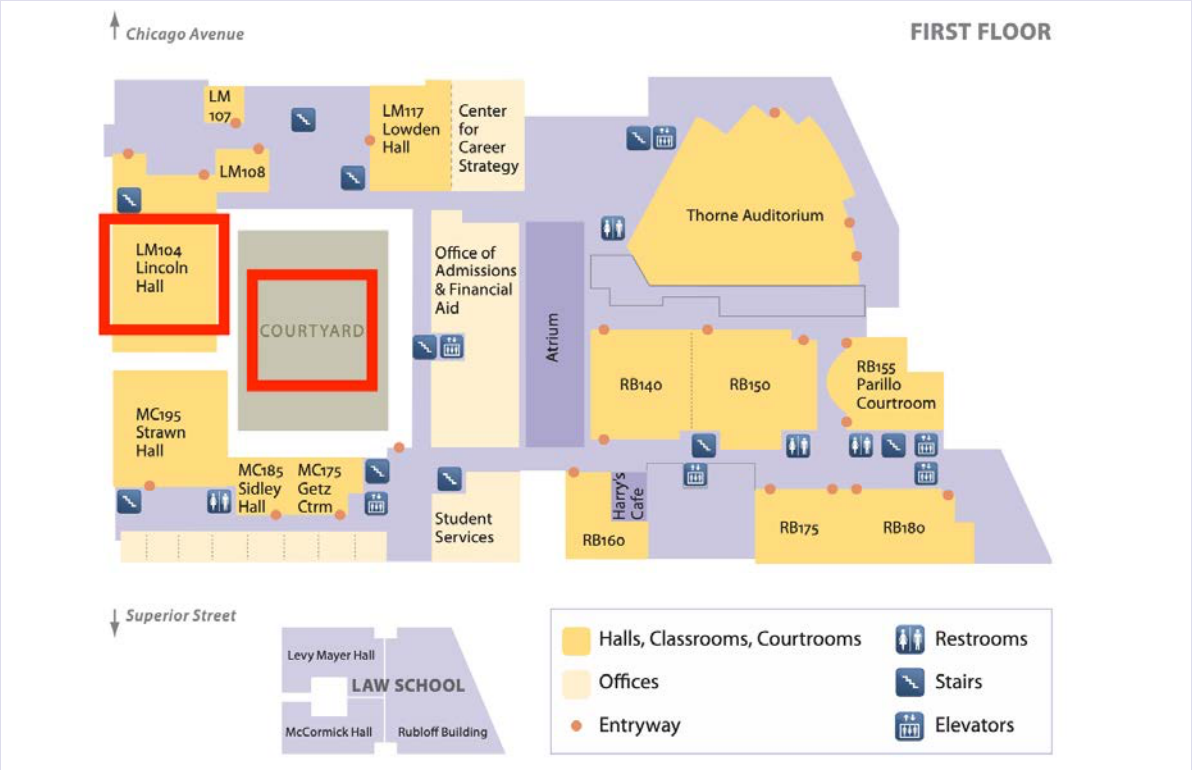

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BMG Retreat Committee: Lillian Eichner, PhD, Assistant Professor, Department of Biochemistry and Molecular Genetics and Clara Peek, PhD, Assistant Professor, Biochemistry and Molecular Genetics, Medicine (Endocrinology)