Friday June 5, 2026

SFH220

9:00 am **Department Chair's Welcome and Introductions – Walter Atwood, Ph.D.**

9:05 am **Biographical Sketch of Dr. Samuel M. Nabrit, Ph.D. – Sebastian Millien**

9:15 am **Keynote Address**
Bil Clemons, Ph.D. (California Institute of Technology)
Killing bacteria by leveraging phage-derived peptide antibiotics

SFH Atrium

10:15 am **Short Break**

SFH220

10:25 am **Tonie Farris, Ph.D. (Duke University)**
Demystifying the role of an E2 ubiquitin-conjugating enzyme UBE2A in neurodevelopment

10:40 am **Sudipta Biswas (Emory University)**
Leiomodin-2 is a processive pointed-end elongator of actin filaments

10:55 am **Novalia Pishesha, Ph.D. (Boston Children's Hospital / Harvard Medical School)**
Engineered nanobodies to direct and visualize immune tolerance

11:10 am **Lightening Talks for Poster Session**
Marissa Berry, Brianna Dominguez, Funsho Ogunshola, Emma Sedivy, Jaime Carazco-Carrillo, Walatta-Tseyon Mesquitta

SFH Atrium

11:30 am **Poster Session**

12:50 pm **Lunch and Informal Poster Viewing**

SFH220

2:00 pm **Luz Porras, Ph.D. (University of Florida)**
Ultrarare structural variant alters 3D genome architecture and gene expression in schizophrenia neural models

2:15 pm **Helen Magana (University of Massachusetts Chan Medical School)**
VPS45 binding sites regulate Rabenosyn-5 and Syntaxin-16 binding in endosomal membrane trafficking

2:30 pm **Joselyn Landazuri Vinueza, Ph.D. (Fred Hutch Cancer Center)**
Understanding the role of δ-catenin in Merkel cell carcinoma tumors caused by Merkel cell polyomavirus

2:45 pm **Rubén García-Reyes (Washington University School of Medicine in St. Louis)**
Navigating appetitive motivation in the Dorsal Raphe through modulation in vGAT, vGlut2 and vGlut3 subpopulations

3:00 pm **Issa Yusuf, Ph.D. (University of Massachusetts Chan Medical School)**
Aberrant protein citrullination characterizes ALS progression and its downregulation protects motor neurons, axons and NMJ and modulates disease outcome in an ALS mouse model

3:15 pm **Amanda Ruiz, Ph.D. (Ragon Institute of MGB, MIT, and Harvard)**
Elucidating immunodominance mechanisms using protein engineering techniques to inform rational vaccine design

SFH Atrium

3:30 pm **Short Break**

SFH220

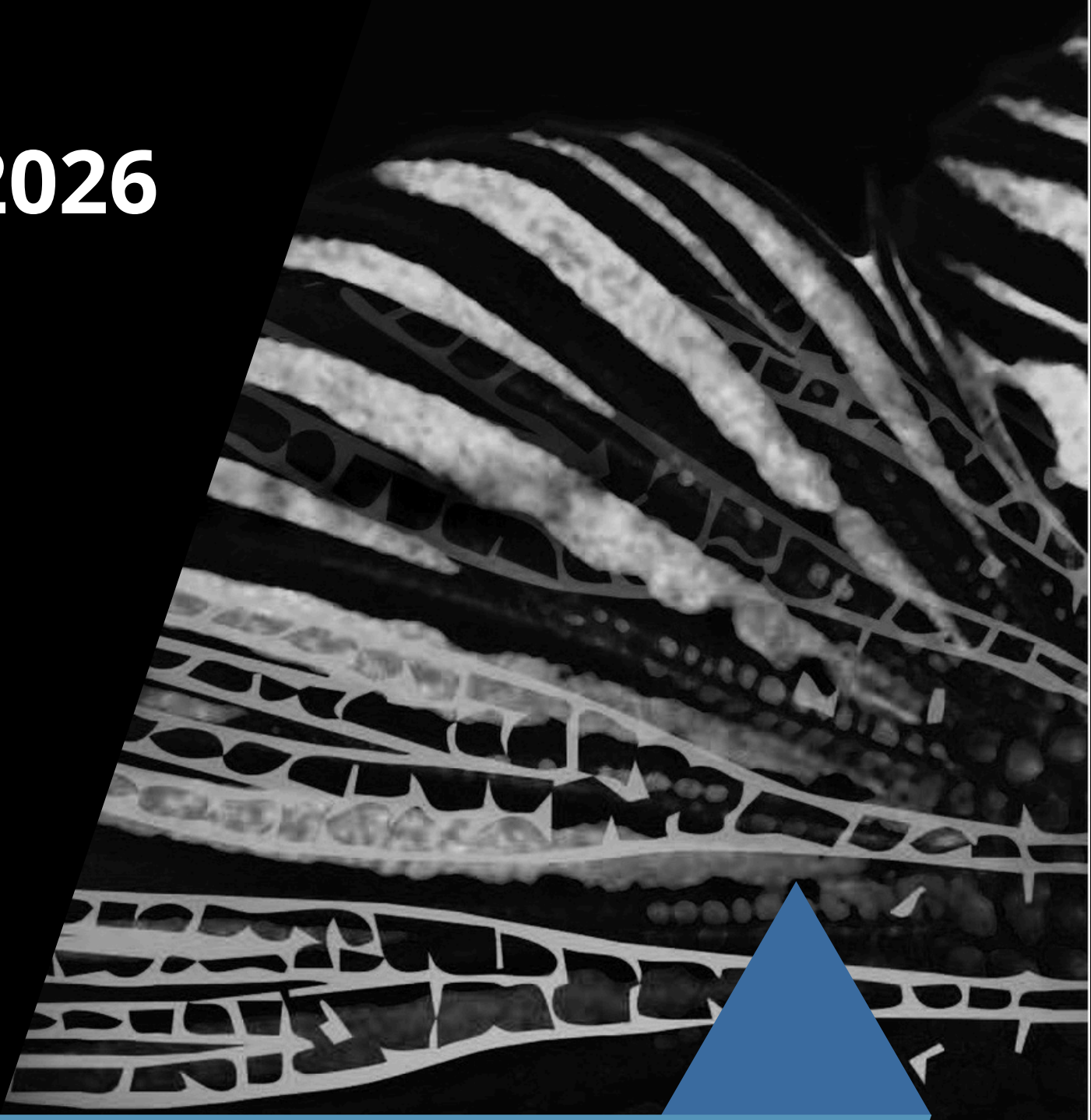
3:40 pm **Early Career Researchers Panel Discussion**
Charting your course
Moderators: Janet Joseph and Sebastian Millien
Panelists: Tonie Farris, Rubén García-Reyes, Helen Magana, Amanda Ruiz
Issa Yusef

5:00 pm **Closing Remarks**

SFH Atrium

5:10 pm **Reception**

2026



8TH ANNUAL

Dr. Samuel M. Nabrit Conference for Early Career Scholars

BROWN

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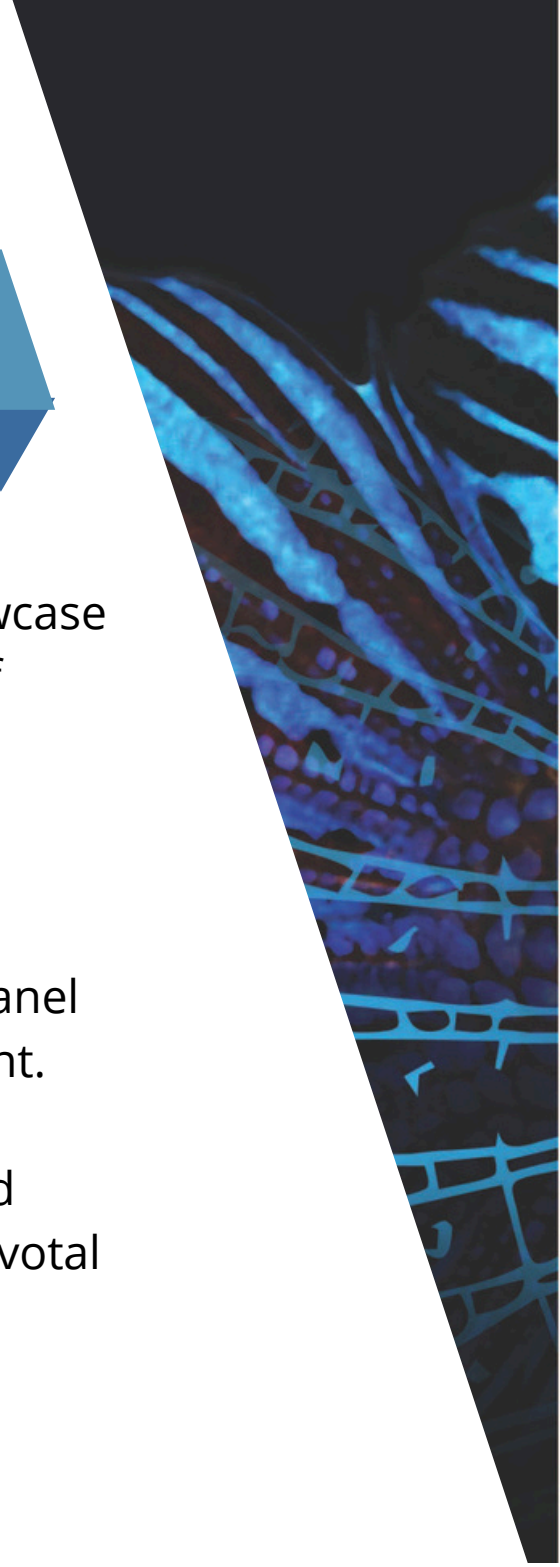
About the Conference



The Nabrit Conference is a platform to showcase and celebrate the research achievements of outstanding molecular life scientists.

The conference features a keynote address, alongside short talks by invited early career scholars, a dynamic poster session, and a panel event dedicated to professional development.

We aim to provide visibility, mentorship, and networking opportunities for scientists at pivotal stages of their careers.

Sponsored by the Department of Molecular Biology, Cell Biology, and Biochemistry and the Office of Diversity and Inclusion at Brown University.

go.brown.edu/nabrit2026

About
Dr. Samuel M. Nabrit

Dr. Nabrit was an internationally distinguished marine biologist who made history as Brown University's first African-American Ph.D. recipient and trustee. He was an influential researcher on tissue regeneration and a stellar academic leader.

His expertise earned him high-level appointments under U.S. Presidents Eisenhower, Kennedy, and Johnson, including roles on the National Science Board and the Atomic Energy Commission.

The Dr. Samuel M. Nabrit Conference for Early Career Scholars celebrates his pioneering legacy.

2026

Keynote Speaker

Bil Clemons, Ph.D.

Killing bacteria by leveraging phage-derived peptide antibiotics

Bil Clemons
Hanisch Memorial Professor of Biochemistry
California Institute of Technology

A vital step in the bacteriophage life cycle is the need to breach the peptidoglycan layer of the bacterial cell wall. Although various lysis mechanisms have evolved, the simplest ones are found in single-stranded DNA or RNA bacteriophages, which, due to their small genomes, encode a single-gene lysis (Sgl) protein. In this talk, I will discuss how we use single-particle electron cryo-microscopy to determine structures of these Sgls bound to their targets, including the essential enzyme MraY and the flippase MurJ. I will explain how these structures have inspired both mechanistic understanding and our efforts to develop new small-molecule inhibitors.

2026
Short Research Talks

Tonie Farris, PhD

Demystifying the role of an E2 ubiquitin-conjugating enzyme UBE2A in neurodevelopment

Tonie Farris, Neil Nimmagadda, Carl Manner, Gustavo Silva
Duke University

UBE2A deficiency syndrome is an X-linked neurodevelopmental disorder that exclusively affects male individuals and is caused by mutations in the UBE2A gene. The most common symptoms observed in the patient population include cognitive disabilities, developmental delays, brain abnormalities, and heart defects, which require patients to have caregiver support throughout their lives. Currently, there is no cure or therapeutic interventions available for patients. Previous studies report that under conditions of stress, UBE2A-deficient cells exhibit mitochondrial dysfunctions including loss of membrane potential and altered mitochondrial morphology. Research further suggests that UBE2A deficiency is associated with deficits in neuronal synaptic plasticity. However, the precise molecular mechanisms by which UBE2A regulates these processes, and how their disruption contributes to disease pathology remain largely unknown. To address this critical knowledge gap, I propose to test the hypothesis that under conditions of cellular stress, loss-of-function mutations in UBE2A impair ubiquitin-dependent regulation of mitochondrial quality control pathways, leading to accumulation of dysfunctional mitochondria and ultimately disrupt neuronal synaptic networks. I will elucidate the role of UBE2A in regulating mitochondrial physiology and determine how these functions impact intracellular signaling in the CNS with the following aims: (1) I will investigate the mechanisms by which UBE2A regulates mitochondrial membrane potential. (2) I will determine how UBE2A modulates the integrated stress response following mitochondrial stress. (3) I will elucidate the mechanism by which UBE2A regulates hippocampal-dependent learning and memory. Overall, this study will advance our understanding of the functional role of UBE2A in neurodevelopment and mitochondrial homeostasis.

2026
Short Research Talks

Sudipta Biswas

Leiomodin-2 is a processive pointed-end elongator of actin filaments

Sudipta Biswas, Shashank Shekhar
Emory University

The actin cytoskeleton drives essential biological processes like cell migration and muscle contraction. While barbed-end polymerization is well-established in vivo, pointed-end elongation was long considered physiologically impossible. Here, we demonstrate that Leiomodin 2 (Lmod2) functions as a processive actin polymerase in thin(actin)-filament pointed ends in striated muscle. Single-molecule and single-filament imaging using Total Internal Refection Fluorescence Microscopy(TIRF) reveal that Lmod2 stably associates with pointed ends in vitro, enabling elongation even under profilin-rich, cytosol-like conditions that otherwise typically promote depolymerization of free pointed ends. Strikingly, Lmod2's activity persists in the presence of tropomyosin, confirming its physiological role. The elongation and processivity are dependent on WH2 domain of Lmod2, a conserved homology domain found in diverse sets of actin nucleators and elongators in cells. Further, a human dilated cardiomyopathy-associated mutation severely impairs Lmod2's polymerase activity, directly linking this mechanism to cardiac dysfunction. Our work establishes pointed-end polymerization as a novel cellular mechanism of actin assembly providing a mechanistic basis for Lmod2-related muscle diseases and challenging the nearly half a century old dogma of actin treadmilling in cells.

2026
Short Research Talks

Novalia Pishesha

Engineered Nanobodies to Direct and Visualize Immune Tolerance

Novalia Pishesha, Priscilla Faas, Stephanie Scharmann, Floris van Dalen
Boston Children's Hospital and Harvard Medical School

Current treatments for autoimmunity and allergy primarily manage symptoms rather than cure disease. We propose a curative nanobody-based approach that selectively silences pathogenic responses to specific antigens or allergens while preserving protective immunity, achieving durable antigen-specific immune tolerance. We also developed nanobody-based imaging tools to map antigen processing and T cell responses in vivo, enabling precise visualization and quantification of tolerance induction at the molecular and cellular levels.

Our approach uses alpaca-derived nanobodies (VHHs) that recognize all MHC class II molecules VHH MHCII. We covalently conjugated disease- or allergen-specific peptides - derived from myelin, insulin, citrullinated collagen, the model antigen ovalbumin (OVA), and house dust mite allergen - to VHH MHCII together with the anti-inflammatory drug dexamethasone, generating trimodal VHH MHCII-antigen(s)-DEX conjugates.

A single dose of these constructs induced durable, antigen-specific tolerance by promoting deletion, anergy, and regulatory differentiation of antigen-specific T cells. VHH MHCII-Myelin-DEX reversed experimental autoimmune encephalomyelitis, VHH MHCII-collagen peptides-DEX halted arthritis progression, and intranasal delivery of VHH MHCII-OVA-DEX reduced OVA-specific IgG and IgE, mast cell activation, and airway inflammation. Tolerance was durable in both prophylactic and therapeutic settings while systemic immunity to unrelated antigens was preserved.

Complementing these therapeutic tools, we developed nanobodies functionalized for fluorescence microscopy and positron emission tomography (PET) imaging to track antigen-specific T cells and visualize antigen processing in real time. Together, these tools reveal how APC networks orchestrate tolerance and establish a modular, low-cost platform for antigen- and allergen-specific immunotherapy. A human-specific VHH MHCII that broadly cross-reacts with human and non-human primate MHC class II alleles enables direct clinical translation.

2026

Short Research Talks

Luz Porras, PhD

Ultrarare Structural Variant Alters 3D Genome Architecture and Gene Expression in Schizophrenia Neural Models

L.M. Porras[1], M. Farrell[2], I. Rodrigue- Lausell[1], G.A. Iglesias-Maldonado[1], C. Leveque1, NE. Ancalade[2], E.V.F. Tuliao[1], G. Martínez[1], P. Giusti-Rodríguez[1*], J.P. Szatkiewicz[2*]

[1]Department of Psychiatry, University of Florida, Gainesville, FL, USA, [2]Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Structural variants (SVs) are increasingly recognized as contributors to schizophrenia risk, yet their effects on 3D genome organization and gene regulation remain poorly understood. We investigated the impact of an ultrarare ~500 kb deletion on chromosome 13 (DEL-chr13), identified in a schizophrenia cohort, using CRISPR/Cas9-engineered isogenic human iPSCs differentiated into neural precursor cells (NPCs), excitatory glutamatergic neurons (EGNs), and medium spiny neurons (MSNs).

We generated high-resolution in situ Hi-C and RNA-seq across these cell types to examine how the deletion alters chromatin architecture and transcriptional programs. Global analyses showed that chromatin organization and transcriptomic profiles clustered primarily by cell type rather than genotype, confirming robust neuronal differentiation. Locally, the topologically associated domain (TAD) boundary overlapping the deletion remained intact across all cell types. However, high-resolution loop analysis revealed the consistent formation of a novel chromatin loop at the deletion site, suggesting regulatory rewiring.

Genome-wide analyses further identified widespread alterations in chromatin compartments, TADs, FIREs, and loops, with ~4–5% of loops affected depending on cell type. These structural changes were associated with differential gene expression enriched in schizophrenia-relevant pathways, including synaptic signaling and neurodevelopment. Integration of loop–gene interactions and RNA-seq highlighted dysregulation of candidate genes such as SLITRK4, PCDHA family genes, NKX6-2, and ARX, particularly in medium spiny neurons.

Together, our findings demonstrate that ultrarare structural variants can reshape 3D genome architecture and transcriptional networks in a cell-type-specific manner, providing mechanistic insight into how SVs contribute to schizophrenia pathogenesis.

2026
Short Research Talks

Helen Magana

VPS45 binding sites regulate Rabenosyn-5 and Syntaxin 16 binding in endosomal membrane trafficking

Helen Magana[1], Melonnie Furgason[1], Roey Chen[2], Peter Newburger[3], Mary Munson[1]
[1]Biochemistry and Molecular Biotechnology Department, University of Massachusetts Chan Medical School, Worcester, MA, 01605, [2]Department of Chemistry & Biochemistry, Worcester Polytechnic Institute, Worcester, MA, 01609, [3]Department of Pediatrics, University of Massachusetts Chan Medical School, Worcester, MA, 01605

Membrane trafficking is required for cell growth, secretion, signaling, and survival. Many proteins regulate vesicle trafficking and ensure cargo is delivered to the correct place at the appropriate time. SNARE proteins, located on the vesicle and target membranes (v-SNAREs and t-SNAREs, respectively), control membrane fusion through the assembly of a four-helix SNARE complex. VPS45, a Sec1/Munc18 (SM) protein, is a regulator of endosomal membrane trafficking through its interaction with SNARE proteins. Point mutations in VPS45 are also associated with Severe Congenital Neutropenia 5 (SCN5), a devastating disease. VPS45 binds the syntaxin type t-SNARE, Syntaxin 16, through two binding modes. The first interaction site is between the N-peptide of Syntaxin 16 and a hydrophobic pocket in VPS45. The second binding mode involves the cleft of VPS45 and the Habc domain and SNARE motif of Syntaxin 16. It is hypothesized that the interactions between VPS45 and Syntaxin 16 regulate membrane fusion. VPS45 also interacts with the endosomal Rab5 effector, Rabenosyn-5. The function of this complex and its role in membrane trafficking is currently under investigation. Using recombinantly expressed, purified proteins, we examine interactions, and any possible competition, between VPS45, Rabenosyn-5, and Syntaxin 16. We are testing the role of the VPS45 hydrophobic pocket in these interactions using a variety of VPS45, Rabenosyn-5, and Syntaxin 16 mutants. Additionally, the wildtype mechanism and modes of interaction will elucidate the dysfunctional VPS45 SCN5 mechanisms.

2026
Short Research Talks

Joselyn Landazuri Vinueza, PhD

Understanding the role of δ-catenin in Merkel cell carcinoma tumors caused by Merkel cell polyomavirus

Landazuri Vinueza J., Salisbury N., Dye K., Roman A., Galloway D.A.
Fred Hutch Cancer Center

Merkel cell carcinoma (MCC) is a very aggressive neuroendocrine cancer of the skin with limited treatment options though many patients have shown success with PD-1/PDL1 inhibition. There is, therefore, an unmet need to identify new entry points for targeted therapies to treat patients with MCC. MCC is often caused by the integration of Merkel cell polyomavirus (MCPyV) and persistent expression of two viral oncoproteins: small T (ST) and truncated large T (t-LT) antigens. δ-catenin was identified as an interactor with ST by TurboID mass spectroscopy and is expressed as several isoforms. Here, we report that δ-catenin isoform 3 represses HLA-I genes in MKL2, a virus positive (VP) MCC cell line. It has been reported that ST induces the expression of lysine-specific histone demethylase 1A (LSD1) which promotes MCC neuroendocrine characteristics. Besides reducing the neuroendocrine characteristics of MCC, inhibition of LSD1 also leads to the switching of δ-catenin isoform 3 to isoform 1 in MKL2 cells. Additionally, we found that inhibition of LSD1 decreases the expression of epithelial splicing regulatory protein 1 (ESRP1), which is responsible for the switch from δ-catenin isoform 3 to isoform 1. Knock down of LSD1 confirmed the pharmacological inhibitor-based results. Knocking down δ-catenin in MKL2 revealed that δ-catenin represses the expression of antigen presentation machinery genes. Based on these data, we propose that ST induces the expression of LSD1, which regulates ESRP1 expression and promotes the expression of δ-catenin isoform 3, repressing HLA-I gene expression. The combination of LSD1 inhibitors with checkpoint inhibitors may represent a promising treatment strategy for patients with MCC.

2026
Short Research Talks

Rubén García-Reyes

Navigating appetitive motivation in the Dorsal Raphe through modulation in vGAT, vGlut2 and vGlut3 subpopulations

Rubén A. García-Reyes, Hajin Ruy, Bhavya Agarwal, Daniel Castro
Washington University School of Medicine in St. Louis

The dorsal raphe nucleus (DRN) is a neuromodulatory divergent hub for appetitive motivation. We characterized DRN vGAT, vGlut2 and vGlut3 subpopulations to understand how they regulate reward. Previous work has shown that vGAT and vGlut3 neurons oppositely enhance or suppress reward, respectively. But whether this extends to other types of reward, and how vGlut2 neurons further impact behavior remains unknown. To test the function of each subpopulation, we chemogenetically stimulated each cell type during food intake, social interaction or open field assays. We found that chemogenetic activation of DRN vGAT cells significantly increased food intake under both ad libitum and food deprived states, primarily by increasing meal size. For social interaction, vGAT stimulation had no overall effect on time spent with a novel conspecific, but did increase the duration of investigative bouts, like meal size. Finally, vGAT stimulation decreased distance traveled in the open field without altering center entries or time in the center. Unlike vGAT stimulation, DRN vGlut2 and DRN vGlut3 cell activation significantly reduced ad libitum and food deprived intake. Time spent with a novel stimulus was also significantly reduced for both cell types. However, only activation of vGlut2 cells significantly reduced the number of interactions leading to shorter investigative bouts in comparison to vGlut3. Lastly, activation of either DRN vGlut2 or vGlut3 cells led to significantly reduced locomotor activity and fewer entries into the center zone. Our findings suggest a complimentary DRN-based microcircuit with distinctive tuning for appetitive responses in both food and social reward.

2026
Short Research Talks

Issa Yusuf, PhD

Aberrant protein citrullination characterizes ALS progression and its downregulation protects motor neurons, axons and NMJ and modulates disease outcome in an ALS mouse model

Issa O. Yusuf, Webb Camille, Paul R. Thompson, Zuoshang Xu

Department of Biochemistry and Molecular Biotechnology, University of Massachusetts Chan Medical School, Worcester, MA, USA

Protein citrullination (PC) is a posttranslational modification involving the conversion of protein-arginine to protein-citrulline and is catalyzed by a family of enzymes known as protein arginine deiminases (PADs). Mammals encode five PADs, and PAD2 is the most dominant in the central nervous system. We demonstrated in transgenic mice and humans that aberrant citrullination and PAD2 dysregulation characterized astrogliosis and myelin protein aggregation in amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease characterized by motor neurons loss, and paralysis. We mapped out the entire citrullinome of mice spinal cord and found that citrullination is increased in glia cells while decreasing in neurons in ALS. We hypothesized that dysregulated PAD2 and PC contribute to ALS pathogenesis. To test this hypothesis, we generated PAD2-knockout (PAD2KO)-SOD1G93A ALS mice and examined consequent modulation on clinical symptoms and pathology. Analysis revealed that the body weight peaked about 3 weeks earlier than the SOD1G93A ALS mice, suggesting that PAD2KO accelerated the disease. However, the disease progression was slowed, leading to longer survival in males. Cellularly, PAD2KO preserved myelin, axons, neuromuscular junctions (NMJs), and motor neurons. Furthermore, PAD2KO reduced PC and myelin protein MBP aggregation. Using antibodies against different MBP citrullinated sites, we found that citrullination at arginine residue 24 (R24) was enriched in the myelin aggregates in ALS mice. PAD2KO eliminated R24 citrullination and reduced MBP aggregation, suggesting PAD2 citrullinate R24, which in turn facilitates MBP aggregation. Taking together, our results demonstrate that PAD2-mediated citrullination plays a role in ALS pathogenesis through MBP aggregation and myelin degeneration.

2026
Short Research Talks

Amanda Ruiz, PhD

Elucidating immunodominance mechanisms using protein engineering techniques to inform rational vaccine design

A.E. Ruiz[1,2,3,4], L.R. Evanson[3,4,5], A-S. Boguraev[3, 4,6], A. Garavito[3,4,6], D.T. Lamson[3,4], G. Ospina[3,4,5], A.G. Schmidt[3,4]

[1] Koch Institute for Integrative Cancer Research, Cambridge, MA, USA, [2] Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA, [3] Ragon Institute of Mass General, MIT, and Harvard, Cambridge, MA, USA, [4] Department of Microbiology, Harvard Medical School, Boston, MA, USA, [5] Virology PhD Program, Harvard University, Cambridge, MA, USA, [6] Chemical Biology PhD Program, Harvard University, Cambridge, MA, USA

Background: Flaviviruses cause significant global morbidity and mortality, yet licensed vaccines exist for only a small fraction of the more than forty species that infect humans. Next-generation vaccine strategies aim to elicit antibodies targeting conserved epitopes on the envelope (E) protein, particularly domain III (DIII). However, these responses are often subdominant to variable immunodominant epitopes, highlighting a limited understanding of how structural constraints shape immunodominance and how antibody responses can be redirected toward protective targets.

Methods: We engineered flavivirus immunogens using epitope scaffolding to elicit conformation-specific, broadly neutralizing antibodies (bnAbs) targeting conserved regions on E-DIII. Specifically, we focused on the lateral ridge epitope recognized by bnAbs T025 (tick-borne encephalitis virus, TBEV) and E16 (West Nile virus, WNV). Fourteen No Known Vector (NKV) flaviviruses were screened as potential E-DIII scaffolds. Candidate scaffolds were optimized using yeast display and evaluated for their ability to focus immune responses to conserved epitopes in vivo.

Results: Key contact residues from TBEV and WNV E-DIII were successfully grafted onto NKV-derived scaffolds. Three resurfaced scaffolds—rsBatu Cave virus and rsPhnom Penh virus (TBEV), and rsApoi virus (WNV)—were prioritized and affinity matured. Recombinant proteins demonstrated binding to bnAbs comparable to wild-type E-DIII by BLI and ELISA. Mouse immunization studies were completed to assess B cell responses targeting grafted epitopes.

Conclusion: This work establishes a structure-guided framework to interrogate flavivirus immunodominance. By isolating conserved neutralizing epitopes on heterologous scaffolds, this approach enables mechanistic evaluation of how structural features shape antibody responses and informs rational vaccine design targeting subdominant, conserved epitopes.

2026

Poster Abstracts

Tolulope Adewumi

1

Understanding the Effects of BIA on Blood-Brain Barrier Penetration in Pediatric Glioma Models

Tolulope Adewumi, Jasmine Clark, Philippa Vaughn-Beaucaire, Sean Lawler

Legorreta Cancer Center, Department of Pathobiology and Laboratory Medicine, Department of Therapeutics, Brown University

Pediatric high grade gliomas (pHGG) are aggressive childhood brain tumors with no effective treatments with a median survival rate of just 10 months. Extensive invasion into normal brain tissue makes surgical removal impossible. The major hurdle in effective drug administration for pHGG is the impenetrability of the blood-brain barrier (BBB) which protects the brain from most therapeutic agents. Further complications are the location of many pHGGS in the pons and lack of preclinical in vivo models for translational studies. We previously showed that Bio-acetoxime (BIA), a derivative of the traditional Chinese medicine Indirubin, can cross and disrupt the BBB and also has antimigratory effects in glioma cells at 1μM BIA. We evaluated the effects of BIA on pediatric glioma cells using viability assays and flow cytometry to determine the effects of BIA on DIPG36 and SF8628 pHGG cell lines in vitro. These assays demonstrate BIA's effects on DIPG36 & SF8628 pHGG cell lines in vitro by reduced viability (IC50 = 1.2 μM DIPG36 & 1.8 μM SF8628) and reduced cell cycle progression arresting cells in the G0 and G1 phase. Also, BIA treatment was associated with disruption of endothelial barrier integrity, increasing BBB permeability. 3D BBB spheroids investigated permeability and their fluorescence shows the barrier disrupting effects of BIA after 24 hour drug treatment. BIA treatment reduced endothelial barrier integrity as measured by a decreased transendothelial electrical resistance (TEER). Potentially, BIA is treatment of pHGG by improving drug delivery through the BBB & future experiments will determine potential in vivo.

Shivmani Barve

2

Lipid Nanoparticle Optimization with Cationic lipids, Phospholipids and Target Cell-derived Lipid Extract improves Cellular Interaction and Drug Effects for Chronic Myeloid Leukemia in vitro

Shivmani Barve, Robert B. Campbell, PhD

Massachusetts College of Pharmacy and Health Sciences

Background: Lipid Nanoparticles (LNPs) have been established as excellent vehicles for drug delivery for Chronic Myeloid Leukemia (CML). The optimization of lipid ratios of cationic lipids and helper lipids like Phosphatidylcholine and Phosphoethanolamine governs the LNPs' selectivity. Furthermore, the incorporation of lipid extracts (LE) derived from target cell membranes has been used to improve targeting. In this study, we investigate the cellular interactions of LNPs consisting of phospholipids with different combinations of cationic lipids and LE using a CML cell line.

Methods: LNPs were prepared using the thin film hydration method. Phase I compared the cellular uptake of LNPs, substituting four cationic lipids at varying concentrations with helper lipids DOPC or DOPE. Phase II investigated the cellular uptake of LNPs after inclusion of LE at various concentrations by target and non-target cell lines and the subsequent drug effects. Results: Overall, the cellular uptake was approximately 250% higher for optimized cationic LNPs compared to the control in Phase I. In Phase II, the inclusion of CML cell-derived LE in the cationic LNPs led to selective uptake by the target (CML) cell and decreased uptake by control cells. LE-modified LNPs displayed selective targeting and superior nano-formulation drug effects. Discussion: Inclusion of CML-LE in LNPs caused greater cytotoxicity against target cells while causing no additional off-target drug effects. Conclusion: Results revealed that cellular uptake of LNPs depends largely on the optimum ratio of the cationic lipid to the helper lipid type, and that inclusion of LE leads to superior targeting.

2026 Poster Abstracts

Marissa Berry

3

Investigating the specificity of bacterial anti-sigma factors

Marissa A. Berry[1], Meng S. Choy[2], Yunyue Wang[1], Jai J. Tavera[1], Wolfgang Peti[2], and Oriana S. Fisher[1]

[1]Wesleyan University Department of Molecular Biology and Biochemistry Middletown, CT, [2]UCONN Health Department of Molecular Biology and Biophysics Farmington, CT

Kinases play a key role in bacterial signal transduction by conveying signals across cells through phosphorylation events. This allows bacteria to adapt to their environments, withstand stressors, invade their host, and activate virulence. Anti-sigma factors are a widely distributed class of kinase that structurally resemble the kinase domain of a histidine kinase but phosphorylate serine residues. Within the model organism Bacillus subtilis, two structurally homologous Anti-sigma factors called SpoIIAB and RsbW regulate sporulation and the general stress response. We hypothesize that differentially conserved residues between lineages of Anti-sigma factors dictate specificity. Through computational analysis, we have determined that SpoIIAB and RsbW represent two distinct lineages of Anti-sigma factors. These results were consistent across both phylogenetic analysis and sequence-similarity clustering. We then identified differentially conserved amino acid residues between these two lineages and investigated their effects on the binding affinity of Anti-sigma factors in vitro using Surface Plasmon Resonance. We found that residues outside the catalytic site are required for the interaction between the Anti-sigma factors and their cognate substrates. Our results therefore provide insight into the evolutionary relationship between SpoIIAB and RsbW and their substrate specificity.

Elizabeth Carrara

4

PIM1 Kinase as a Regulator of Aggressive Phenotypes in Cancer Effects of Pharmacological Inhibition on Survival and the Tumor Microenvironment

Elizabeth Carrara, Sean Lawler, Sheldon Holder

Brown University

Cancer progression is driven by mechanisms that promote cell survival, invasion, and interaction with the tumor microenvironment (TME). The serine/threonine kinase PIM1 has been implicated in these processes; however, its role in aggressive solid tumors such as triple-negative breast cancer (TNBC) and glioblastoma (GBM) remains unclear. This study evaluated the role of PIM1 in epithelial–mesenchymal transition (EMT), tumor cell survival, migration, and tumor–immune interactions.

A combination of bioinformatic and experimental approaches was used. Public datasets were analyzed to assess PIM1 expression, survival outcomes, and co-expression with oncogenic markers. In vitro experiments were performed using TNBC and GBM cell lines treated with PIM1 inhibitors SGI1776 and TP3654. Cell viability was measured by MTT assays, migration by wound healing assays, and protein expression by western blotting. Co-culture systems with T lymphocytes were used to investigate tumor–immune interactions.

Bioinformatic analyses showed no significant association between PIM1 expression and survival in TNBC, whereas GBM exhibited elevated PIM1 expression correlated with poorer survival. Experimentally, PIM1 inhibition reduced cell viability and migration in GBM and decreased pro-survival signaling. In TNBC, PIM1 expression decreased following EMT induction, suggesting a context-dependent role. Co-culture experiments indicated that PIM1 inhibition altered tumor–immune interactions, increasing cellular aggregation.

PIM1 plays a context-dependent role in cancer progression, with a more prominent functional significance in GBM than in TNBC. These findings support the potential of PIM1 as a therapeutic target in GBM and highlight its role in both tumor-intrinsic signaling and tumor microenvironment dynamics.

Jaime Carrazco-Carrillo

5

A novel role for the cuproprotein Csrp2 in skeletal muscle proliferation, differentiation and regeneration

Jaime Carrazco-Carrillo[1], Arpie Bakhshian[1&], Monserrat Olea-Flores[1,2&], David C. Klein[3,#], Anand Parikh[1], Natalie O'Neaill[4], Martha L. Jiménez-González[5], Aidan T. Pezacki[6,7], Christopher J. Chang[6,7], Luis Antonio Ortiz-Frade[5], Juan G. Navea[4], Sarah J. Hainer[2], Teresita Padilla-Benavides[1*]

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Copper (Cu) is a critical trace element required for cellular function, yet toxic when unregulated. Cu homeostasis, or cuprostasis, relies on a complex network of transporters, chaperones, and regulatory proteins. While the roles of Cu-binding proteins (Cu-BPs) in enzymatic catalysis and redox balance are well known, emerging evidence points to their unexpected involvement in gene regulation. We have identified a novel function for the Cu-binding protein cysteine- and glycine-rich protein 2 (mCsrp2) in skeletal muscle biology using murine primary myoblasts as a model system. Using an unbiased synchrotron X-ray fluorescence/mass spectrometry (XRF/MS) metalloproteomics pipeline, we discovered mCSRP2 in a Cu-enriched protein fraction from differentiating satellite cell-derived myoblasts. Biochemical and electrochemical analyses confirmed that human CSRP2 (hsCSRP2) binds Cu+ with high affinity and exhibits redox activity. We found mCSRP2 to be localized predominantly in the nucleus with some cytosolic expression, and expression decreasing upon differentiation. Functional studies revealed that CRISPR/Cas9-mediated deletion of mCsrp2 accelerates cell cycle progression and impairs terminal differentiation, pointing to a role in coordinating cell cycle exit during myogenesis. Interestingly, mCsrp2 knockout myoblasts show increased intracellular Cu, particularly Cu2+, suggesting a role in metal buffering or trafficking. Chromatin profiling (CUT&RUN) revealed mCsrp2 binding to genomic DNA in proliferating myoblasts, and transcriptomic analyses indicate that mCsrp2 deletion dysregulates key cell cycle genes. In vivo muscle regeneration assays demonstrated nuclear expression of mCsrp2 in regenerating myofibers. These findings reveal a previously unrecognized cuproprotein-mediated mechanism that integrates metal homeostasis with gene regulation during skeletal muscle regeneration.

Brianna Dominguez

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Understanding the role of Shigella produced Pic during intracellular host infection

Brianna Dominguez, Mario Meza-Segura, Beth A. McCormick
University of Massachusetts Chan Medical School

Shigella is a human-adapted pathogen responsible for millions of diarrheal infections worldwide. Its impact is increasing due to multidrug resistant strains and limited treatment options. Its ability to evade immune detection within host cells highlights the urgent need for innovative, targeted therapies. Before establishing an infection in the colon, Shigella is engulfed by resident macrophages via phagocytosis but escapes degradation by inducing inflammatory cell death. Following release into the lamina propria, Shigella invades intestinal epithelial cells, where it evades immune detection, replicates and spreads to neighboring cells. We recently identified a secreted Shigella-produced serine protease Pic that may be involved during host escape, targeting cytosolic proteins that govern cellular responses to infection in macrophages and epithelial cells. Our studies demonstrate that purified Pic can efficiently cleave human galectin-3 and galectin-4 in vitro. Galectin-3 and galectin-4 are β-galactoside binding proteins that sense intracellular bacteria: galectin-3 binds host-glycans exposed in the cytosol following bacteria-induced vacuolar rupture, whereas galectin-4 binds LPS to restrict bacterial motility. We thus hypothesize that Shigella produced Pic promotes immune evasion in macrophages and epithelial cells via the cleavage of galectin-3 and galectin-4. To test this, we infected macrophage and intestinal epithelial cells with wildtype Shigella and observed a reduction in galectin-3 and -4 levels. This reduction was rescued in host cells infected with Δpic Shigella, suggesting that the low galectin levels are due to cleavage by Pic. Ultimately, these studies will advance our understanding of Shigella pathogenesis and aid in the development of innovative strategies against Shigella infections.

David Firer

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A genomic view of hypermutation potential in Candida auris drug resistance

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Background: *Candida auris* is a globally emerging pathogen causing life-threatening infections with unusually high rates of multidrug resistance. A potential driver of drug resistance evolution is hypermutation, wherein isolates exhibit elevated mutation rates due to dysfunctional DNA repair mechanisms, including mismatch repair (MMR). This elevated rate may lead to the accumulation of mutations conferring drug resistance. Global characterization of *C. auris* hypermutation is therefore essential to understanding the rapid emergence of multidrug resistance.
Methods: Phylogenies were resolved for 800 clinical isolates with published drug resistance data, spanning all six *C. auris* clades. Candidate hypermutants were identified through variant analysis to detect deleterious MMR gene mutations, and signatures of elevated mutation rates, including larger tip-to-root distances and overrepresentation of private mutations. Drug resistance profiles were mapped to candidates in clinically severe clades (I, III, and IV) to assess the contribution of hypermutation to resistance.
Results: 179 candidate hypermutants harbouring frameshift or nonsynonymous MMR gene mutations were identified across all clades except clade II. Candidates from clades I and III, but not IV, were associated with increased multidrug resistance. Furthermore, candidates from clades I, III, and IV were associated with increased amphotericin B resistance, but not fluconazole or micafungin resistance.
Conclusion: This study offers novel insights into the distribution of hypermutation across *C. auris* clades using innovative identification methods and reveals associations of hypermutation with increased amphotericin B and multidrug resistance. Ultimately, this study lays the groundwork necessary for understanding the relationship between hypermutation and drug resistance in *C. auris.*

Kevin LoGiudice

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Graduate Student Council (GSC) of Brown University

Kevin LoGiudice and Dominique Walker
Brown University

The Graduate Student Council (GSC) of Brown University is the student government organization for Brown's graduate student community of approximately 3,000 members. Our primary aims are to foster a sense of community among graduate students across departments, to facilitate collective action on graduate student-related issues, and to be a voice for the graduate community within the University and the Providence area. We also provide events and resources to support the academic and social lives of Brown graduate students.

Christopher J. Woodilla

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Protamine PTMs generate heterogeneous chromatin states and finetune reproductive fitness

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Traditionally, the sperm genome is thought to be packaged by protamines into a uniformly compact and inert chromatin structure. Here, we challenge this long-standing view by demonstrating that protamine post-translational modifications (PTMs) present on distinct protamine molecules create discrete protamine-DNA chromatin states, ranging from weak to tightly associated chromatin configurations. Loss of these modifications alters protamine-DNA interactions in vitro and in vivo, compromising sperm chromatin integrity and impairing fertility. Therefore, these findings demonstrate that protamines do not merely serve as inert packaging proteins; rather protamine PTMs establish functional heterogeneity within sperm chromatin, creating compartment-like domains analogous to those in somatic cells. Thus, PTMs allow protamines to do more than simply compact the paternal genome—they likely encode a molecular blueprint that orchestrates the timely unpacking and reorganization of the paternal genome after fertilization.

Yiyu Zheng

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Identification and functional characterization of P113 as a novel blood-stage vaccine target against severe plasmodium falciparum malaria

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Malaria remains a leading cause of child mortality, and severe malaria (SM) carries a 20% case fatality rate. Current pre-erythrocytic vaccines (RTS,S/AS01, R21/Matrix-M) have limited efficacy against SM because they do not target blood-stage parasites. Because naturally acquired SM immunity is antibody-mediated and develops after one or two episodes, this study aimed to identify the antigens targeted by these protective antibodies.
Whole-proteome differential screening (WPDS) using post-SM plasma from a Kenyan cohort and a P. falciparum 3D7 cDNA T7-phage library identified 46 candidate antigens. PfP113 (PF3D7_1420700) was prioritized based on enrichment, biochemistry, and biological role: it is a 112.6-kDa GPI-anchored merozoite surface protein that anchors the PfRh5 invasion complex and shows limited sequence variation. PfGARP, a previously validated Kurtis Lab target, served as an internal positive control (34.4% of fourth-round clones).
Recombinant P113 was expressed in Expi293F cells, purified by Ni-IMAC, and confirmed by LC-MS/MS. BALB/c mice immunized with P113 plus TiterMax Gold developed anti-P113 antibodies, but only ~20% of sera (n=45) showed growth-inhibitory activity against P. falciparum 3D7 in vitro. Inhibitory and non-inhibitory sera had comparable titers and equivalent native P113 recognition by Western blot, indicating that inhibition is not determined by antibody quantity. Epitope mapping revealed that inhibitory sera uniquely recognized a shifted epitope, HLQGSEQSIEASESS, implicating it as the functional inhibitory region.
These findings functionally validate P113 as a blood-stage vaccine candidate and identify a candidate inhibitory epitope, establishing a foundation for focused peptide–conjugate immunization and multi-antigen vaccine development against severe P. falciparum malaria.

Flora Wang

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Characterizing the binding capability of a bacterial single-domain kinase

Flora Wang, Marissa Berry, Jai Tavera, Oriana S.Fisher
Department of Molecular Biology & Biochemistry, Wesleyan University

Bacterial signal transduction pathways commonly involve histidine kinases (HKs) to regulate a diversity of cellular processes. While structurally homologous to the kinase domain of HKs, HK-like serine threonine kinases (HK-like STKs) are single-domain kinases without a separate substrate specificity domain. In Bacillus subtilis, there are two HK-like STKs that respectively regulate sporulation and the stress response by phosphorylating their cognate substrates. Previous studies identified conserved residues proposed to mediate interactions between HK-like STKs and their cognate substrates. We initially hypothesized that HK-like STKs exhibit strict substrate specificity that prevents stable binding to non-cognate substrates. However, results from biochemical pulldown assays and size exclusion chromatography showed that one of the HK-like STKs can interact with a non-cognate substrate in addition to its cognate substrate. This suggests that these enzymes are not exclusively specific for their cognate substrates. These findings highlight a need to test whether the interaction between the HK-like STKs and non-cognate substrate occurs in vivo. They also lay a foundation for future analysis to understand specificity determinants and evolutionary relationships across HK-like STKs.

Ines Wang

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Genetically Modified CXCR4-Overexpressing Human Tenocytes as a Cell-Based Therapeutic Strategy for Tendon Repair

Ines Wang, Jay Trivedi, Salomi Desai
Department of Orthopaedics, The Alpert Medical School of Brown University/Rhode Island Hospital

Patellar tendinopathy is a chronic degenerative condition characterized by pain, impaired function, and limited healing capacity due to tenocyte loss and disrupted regenerative signaling. At the molecular level, stromal cell-derived factor-1 (SDF-1) is upregulated in damaged tendon tissue and recruits reparative cells through the C-X-C chemokine receptor type 4 (CXCR4) axis. CXCR4-mediated cell migration is critical for tissue repair, as recruited progenitor cells undergo tenogenic differentiation and promote extracellular matrix (ECM) remodeling. However, excessive tenocyte loss in degenerative patellar tendinopathy results in incomplete tendon repair. Prior work by our group demonstrated improved wound healing following CXCR4-enhanced cell therapy in a rabbit meniscus model, suggesting broader regenerative potential.

We hypothesized that CXCR4 overexpressing human tenocytes would exhibit enhanced retention within the injury microenvironment, and improve tendon healing. To test this, we established a human tenocyte cell line constitutively overexpressing CXCR4 using third-generation lentiviral vectors. Overexpression was confirmed by fluorescence imaging, and further assessed through transcriptomic analysis. RNA sequencing was performed to evaluate changes in the transcriptomics landscape and preservation of the tenocyte phenotype, followed by RT-qPCR and Western blot validation of target pathways.

Ongoing studies include in vitro evaluation of angiogenesis, ECM remodeling, and immunomodulation, as well as in vivo assessment in a collagenase-induced rat patellar tendinopathy model treated with local cell injections. Serial blood and knee joint collection will support analyses of therapeutic cell retention, histologic repair, and molecular remodeling. This work aims to define the regenerative potential of CXCR4-enhanced tenocytes and support their translational application for degenerative tendon disorders.

Iz Varghese

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Characterizing the Role of Symmetry in Macrophage Migration Inhibitory Factor (MIF)

Iz Varghese[1], Jimin Wang[2], Brenda Rubenstein[1], George Lisi[1]
[1]Brown University, [2]Yale University

Macrophage Migration Inhibitory Factor (MIF) is a pro-inflammatory cytokine implicated in numerous rheumatic and inflammatory diseases, including but not limited to various forms of cancer, asthma, arthritis, and lupus. Structurally, MIF is a homotrimer comprised of 12.5 kDa monomers organized around a central solvent channel. Despite its compact arrangement, MIF exhibits diverse biological activities, including receptor binding and activation, enzymatic activity, and insulin chaperoning. Prior work in our lab has linked the pleiotropic nature of MIF to conformational plasticity and allosteric regulation. However, the role of conformational plasticity and allostery in modulating the global symmetry of the protein remains unclear. Thus, this work will provide insight into ongoing efforts to develop a biophysical map of residues in MIF that are critical to stabilizing a symmetric trimer. Preliminary data from computational simulations reveal subtle asymmetries at the trimer interface, suggesting these residues may play a key role in maintaining a stable trimer. Site-directed mutagenesis of these positions results in significant changes to the structural, dynamic, and functional properties of MIF, as characterized by nuclear magnetic resonance (NMR) spectroscopy. Notably, our findings raise the possibility of a stable asymmetric configuration of MIF in solution, which has not been previously characterized. These insights provide a novel framework by which MIF can be regulated. Insights from this project will thus be critical in informing future therapeutic developments that specifically target MIF.

Kai Vestergaard

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Loss of UBE3A Disrupts Ribosomal Biogenesis Pathways: Transcriptomic Insights into Angelman Syndrome

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Angelman Syndrome (AS), a severe neurodevelopmental disorder associated with developmental delay, seizures, and speech impairment, is caused by loss-of-function mutations in the maternally inherited allele of UBE3A, a neuronal ubiquitin E3 ligase essential for normal neurodevelopment. While UBE3A is known to regulate ubiquitin-mediated proteostasis, the downstream molecular pathways contributing to AS pathophysiology remain incompletely defined. To characterize transcriptomic alterations resulting from UBE3A loss and identify cellular pathways potentially contributing to neurodevelopmental impairments in AS. To investigate this, we generated a UBE3A knockout (KO) line in HAP1 cells, a haploid human model system that is ideal for precise genomic editing. Bulk RNA sequencing was performed on UBE3A-KO and isogenic wild-type cells to characterize genome-wide transcriptional changes. Differential expression analysis was followed by Gene Ontology (GO) enrichment analysis and evaluation of alternative splicing to identify significantly affected biological processes. Transcriptomic analysis revealed significant downregulation of genes involved in ribosomal biogenesis and rRNA processing. Gene Ontology enrichment highlighted suppression of structural ribosomal constituents and nucleolar factors, suggesting a potential reduction in translational capacity. Differential splicing analysis identified events in several neurodevelopmental genes, including FOXG1 and ASH2L, although the splicing signature was weaker than differential gene expression. These findings suggest that UBE3A deficiency impacts fundamental ribosomal assembly and translational capacity, extending its role beyond proteostasis to core biosynthetic machinery. Loss of ribosomal biogenesis may play a previously underrecognized role in disrupting neuronal development in Angelman Syndrome, underscoring the need to examine this pathway in neural models.

Karly M Stallworth

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Characterizing Behavioral, Immunological, and Neurological Alterations in a VPS45 E238K Mouse Model

Karly M Stallworth[1], Robin S Nathans[1], Josias Soares de Brito[2], Zhiqing Zhu[2], Kristyn Norris[1], Natasha Buwa[1], Melonnie Furgason[1], Peter E. Newburger[2] and Mary Munson[1]

Department of Biochemistry & Molecular Biotechnology, UMass Chan Medical School, Worcester, MA, United States of America

Vesicle trafficking in the endosomal system is controlled by Vacuolar Protein Sorting 45 (VPS45), a member of the Sec1/Munc18 (SM) family. Mutations in the human VPS45 gene are linked to severe congenital neutropenia (SCN) type 5, characterized by bone marrow fibrosis, recurrent life-threatening infections, and early mortality without hematopoietic stem cell transplantation. Neurological deficits such as developmental delay, motor, and visual impairments were exhibited by several patients in relevant case studies. We developed and characterized a novel mouse model of VPS45 neutropenia by CRISPR/Cas9-mediated knock-in of the pathogenic VPS45 E238K mutation. Behavioral testing was also performed to assess potential cognitive, motor, and visual deficits associated with the VPS45 E238K mutation. The VPS45 E238K mouse model reveals the in vivo impact of this mutation, including disruptions in neutrophil number and function, decreased lymphocyte numbers, and significant effects on birth ratios and survival. Ongoing cell biological studies in mouse embryonic fibroblasts (MEFs) are investigating defects in cargo trafficking through the endocytic pathway, while further characterization of the VPS45 E238K mouse indicates alterations across multiple brain cell types. Through investigation of the cellular mechanisms and affected cell populations, we seek to define how the VPS45 mutation drives cellular dysfunction, ultimately guiding therapeutic development.

Rehana Thewarasige

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Investigating the Effects of DLX5 Knockdown on Osteoarthritic Phenotypes in Chondrocytes

Rehana Thewarasige, Salomi Desai, Chathuraka T. Jayasuriya

Department of Biology and Medicine, Brown University, Department of Orthopaedics, Warren Alpert Medical School of Brown University, and the Rhode Island Hospital

Osteoarthritis (OA) is characterized by progressive cartilage degeneration and altered chondrocyte behaviors, including increased hypertrophy and apoptosis. Previous studies from our lab have demonstrated that the transcription factor DLX5 is overexpressed in osteoarthritic chondrocytes compared to non-osteoarthritic controls. Previous studies by our lab (and others) have also postulated that DLX5 plays a central role in OA onset and/or progression. Particularly, DLX5 knockdown in bone-marrow-derived mesenchymal stem cells has been associated with increased expression of hypertrophy and apoptosis markers.

This study aims to determine whether DLX5 knockdown (KD) protects osteoarthritic chondrocytes from disease-associated phenotypes. Primary chondrocytes were isolated from human articular knee cartilage and immortalized through lentiviral hTERT overexpression. Stable DLX5 knockdown was then achieved using lentiviral shRNA vectors. Gene expression analysis was performed using RT-qPCR, while protein expression and phenotypic changes are being evaluated through western blotting and cell viability assays.

An immortalized cell line was successfully established. Furthermore, preliminary RT-qPCR results demonstrated a trend toward reduced DLX5 expression in DLX5 KD cells following lentiviral shRNA transduction. Ongoing studies will further validate knockdown at the protein level and assess the effects of DLX5 suppression on hypertrophic, apoptotic, and cell viability markers. This model may provide a useful platform for studying the molecular mechanisms underlying osteoarthritis and evaluating potential therapeutic targets associated with DLX5.

Dallis Sergio

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Defining the role of synaptic Schwann cell-derived PDGF-A at the NMJ

Dallis Sergio, Natalie Morrell, Rao Zaid Khan, Katherine Kim, Nikhil Kannan, Gregorio Valdez
Brown University

The neuromuscular junction (NMJ) is a chemical synapse between a motor neuron and a skeletal muscle fiber. Proper function of the NMJ is essential for all voluntary movement, from walking to posture maintenance. A distinct population of non-myelinating synaptic glia called perisynaptic Schwann cells (PSCs) exist at the NMJ. While these cells play indispensable roles in the development and maintenance of neuromuscular synapses, the molecular mechanisms underlying their function remain largely unknown. To address this gap in knowledge, our lab sequenced the transcriptome of PSCs for the first time in history and uncovered PDGF-A as a candidate signaling molecule. Using a combination of transgenic mice, immunohistochemistry, confocal microscopy, and behavioral testing, I am working to define the role of PSC-derived PDGF-A in NMJ formation, stability. As such, my research will significantly contribute to our limited understanding of the molecules PSCs use to influence the NMJ.

Riley Harrison

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Uncovering novel functions for sox9a and sox9b in blood brain barrier and CNS development

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Department of Pathology and Laboratory Medicine, Brown University

The blood brain barrier (BBB) is a multicellular structure that facilitates the entry of oxygen and nutrients into the brain while simultaneously restricting the movement of endogenous and exogenous bloodborne substances. BBB dysfunction allows neurotoxic compounds to infiltrate the brain parenchyma and adversely affect brain health. Accordingly, BBB dysfunction is associated with a number of neurological diseases, including Alzheimer's disease, stroke, and multiple sclerosis. Despite the importance of the BBB in brain health, comparatively little is known about the genetic drivers of BBB development and function. SOX9, a high mobility group transcription factor, is implicated in the development of multiple cellular components of the BBB. In the mammalian CNS, Sox9 is necessary for the proper development of astrocytes, which play important roles in CNS angiogenesis, BBB maintenance, and vascular stability. Previous work using sox9a and sox9b mutants suggest conserved functions for these orthologs in gliogenesis; however, these original mutants have large deletions that affect numerous other genes. We generated new sox9a and sox9b mutants and found that both single and double mutants exhibit cerebral hemorrhaging, neurovascular malformations, enlarged ventricles, cerebral edema, disrupted neural network formation, and reduced brain size. Furthermore, we demonstrate that double mutants have impaired development of astrocytes, oligodendrocytes, and neuronal populations. We are currently generating tools for inducible, cell-type specific manipulations to determine the cellular drivers of the observed neurovascular and brain phenotypes. Identifying novel roles for sox9a and sox9b in neurovascular development and BBB maintenance will provide insight into SOX9 functions in brain development and disease.

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Poster Abstracts

Giorgiana Madeline Ursu

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Cadmium exposure in human cells: main targets of toxicity vs cellular defense mechanisms

Giorgiana Madalina Ursu and Anatoly Zhitkovich

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Cadmium (Cd) is a toxic environmental pollulant that poses significant health risks through contaminated dietary and air, soil, water sources. Long-term bioaccumulation of Cd(II) causes damage to the lungs, kidney dysfunction and neurotoxic effects. Cd(II) does not react with DNA but is known to bind to proteins via their SH-groups. However, it is unclear what proteins are preferentially damaged by Cd(II) and whether global or protein-specific damage underlies its toxicity. In human lung and kidney cells, we found that Cd(II) induced accumulation of K48-polyubiquitinated proteins primarily in the cytosol, and nuclear protein SUMOylation was important for the optimal expression of transcriptional targets of the cytosolic NRF2- and HSF1-driven proteostatic responses. Global protein damage was a major cause of Cd(II) toxicity, as inhibition of ubiquitination or proteasomal activity severely impaired survival of cells at otherwise minimally or nontoxic doses, indicating the requirement for efficient disposal of abnormal proteins. We found that newly synthesized proteins were the main group of Cd(II)-damaged cellular proteins that were undergoing proteolytic K48-polyubiquitnation or became denatured as a result of Cd(II)-induced injury. Proteins with high rates of continuing synthesis such as short-lived transcriptional factors or antiapoptotic proteins were especially sensitive to denaturation by Cd(II). Activation of the integrated stress response limiting protein translation rates diminished accumulation of damaged proteins and increased Cd(II) tolerance by cells. Our findings identified damage to newly synthesized proteins as a major cause of global proteotoxicity and cytotoxicity by Cd(II) and revealed a high vulnerability of short-lived proteins.

Heather Valera

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Investigating the implications of Uchl1 deficiency on granulosa cell function and output

Heather Valera, Morgan Woodman-Sousa, Kathryn Grive

Brown University, Women & Infants Hospital

To achieve reproductive fecundity, mammals cyclically develop and ovulate eggs during reproductive years. A growing oocyte is largely quiescent, and receives nutrients, metabolites and mRNAs from an adjacent population of granulosa cells. As the oocyte matures, it signals to granulosa cells to promote proliferation, allowing for further production of metabolites and steroid signals that will eventually trigger ovulation. Female infertility is unexplained in 10-20% of cases, and while oocyte quality is often considered a potential culprit, little is known of the impact of oocyte-granulosa cell crosstalk on fertility outcomes. The Grive lab and others have identified oocyte loss of master proteostasis regulator UCHL1 as yielding a severely subfertile mouse model. Aim 1 of my project utilizes a transgenic, oocyte-specific knockout of UCHL1 to explore the effect of proteostasis loss in the oocyte on the health of granulosa cells. I aim to describe how this resulting phenotype impacts the follicular microenvironment and broader endocrine signaling. We've discovered drastic metabolic changes in granulosa cells to potentially support increased steroid production, as well as systemically high LH possibly promoting anovulation. Through completing this project, we hope to establish a better understood role for granulosa cell dysfunction in conversations of fertility and endocrine health.

Walatta-Tseyon Mesquitta

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Tcf15 reprograms hematopoietic and immune landscape by inhibiting lymphoid emergence and development

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Boston Children's Hospital, Harvard University, IRB Barcelona

The ability of HSCs to self-renew long term is critical to hematopoietic transplant success. Tcf15 is a bHLH transcription factor with critical functions in paraxial mesoderm development, somitogenesis, and stem cell pluripotency that was shown to be indispensable to long term hematopoietic reconstitution. Many genes associated with long-term hematopoietic function exhibit pleiotropic activity beyond the HSC compartment, influencing lineage bias and differentiation, across the hematopoietic hierarchy. However, the activity of Tcf15 within the broader hematopoietic landscape and downstream lineages has not been previously explored. Here we demonstrate that ectopic Tcf15 expression can remodel the hematopoietic and immune landscape. Tcf15 overexpression diverted hematopoietic activity away from T and B lymphoid differentiation pathways, suppressing lymphoid progenitor emergence, and inhibiting T and B lymphoid lineage restriction, in a cell intrinsic manner. Transcriptional profiling revealed that Tcf15 coordinates the silencing of B-cell networks and the Notch–E-protein axis, effectively blocking the transition from multipotent progenitors to the lymphoid lineage Our findings uncover a novel function for Tcf15 as a critical negative regulator whose downregulation is essential for lymphoid lineage commitment and development.

Ella Mohanram

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Exploratory analysis of network connectivity in ASH1L patient-derived neuronal populations

Ella Mohanram, Krishna Amin, Megha Jhanji, Jason Ritt, and Sofia B. Lizarraga
Carney Institute for Brain Science, Brown University; Department of Neuroscience, Brown University; Center for Translational Neuroscience, Brown University; Department of Molecular Biology, Cell Biology, and Biochemistry, Brown University

Mutations in the chromatin modifier ASH1L disrupt epigenetic regulation during brain development, yet the cellular mechanisms by which ASH1L governs neurodevelopment remain poorly understood. To investigate the function of ASH1L in human neurons, the Lizarraga lab generated induced pluripotent stem cells (iPSCs) from patients with ASH1L mutations who present with autism, intellectual disability, and epilepsy. Previous work from our lab suggests that ASH1L regulates a transcriptional and epigenetic node that controls gene programs important for neuronal structure and function. However, much is unknown at the cellular and physiological levels about how specific pathogenic variants in ASH1L lead to the disease phenotypes. Pilot studies using ASH1L patient iPSC-derived neurons seeded onto a multi-electrode array (MEA) suggest that, compared to control neurons, deficits in ASH1L lead to network hyperexcitability that correlates with seizure activity in patients. Further, biochemical analysis suggests that the hyperexcitability phenotype may be related to a potential change in the ratio of excitatory to inhibitory neurons over developmental timescales. To define the mechanisms that may be driving network hyperexcitability, we utilize cross-correlograms to extract coordinated population-level activity from the raw electrophysiological data collected using MEAs. Our current analysis highlights elevated activity over shorter timescales in ASH1L patient iPSC-derived neuronal populations, suggesting hypersynchrony in these cultures and pointing towards potential deficits in synaptic machinery.

Daniel Li

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Trans-phylum single cell orthology reveals conserved ovarian cell states between sea urchin and human

Daniel Li, Nathalie Oulhen, Gary Wessel
Molecular Biology, Cell Biology & Biochemistry, Brown University

Oocytes are produced before birth in women and their abundance and quality decrease overtime until the loss of ovarian functions at menopause. In contrast, animals such as sea urchins retain stem cells that enable a continuous, high fecundity production of quality oocytes throughout their lifespan. We hypothesize that the somatic cells required for these two different adult ovarian functions are distinct. Comparing sea urchin adult ovaries with human fetal ovaries may reveal greater conservation, since they are both in a state of active oocyte production. Here, we present the first integration of the sea urchin adult ovary with the human fetal and adult ovary single cell RNA-seq datasets. Using SAMap, the resulting integration demonstrates high conservation of cell states and gene expression in both the somatic cells (such as immune and muscle cells) and the germ cells of the ovary. Whereas multiple cell states change over time in the human ovary during its transition from fetal to adult stages, the sea urchin adult ovary instead represents an intermediate state that preserved most of the cell states characteristic of both the fetal and adult human ovary. Comparing reproductive strategies and ovarian function separated by 540 million years since their last common ancestor could lead to new approaches to treat human reproductive senescence. Our results highlight the potential of the sea urchin as a powerful comparative model that lacks reproductive senescence to better understand the cellular transitions underlying the aging human ovary.

Miguel Martinez Guzman

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Characterization of Sso7d-based glycan binding protein's determinants of ligand recognition

Miguel Martinez, Helen B. Belato, Isabelle Nagle, Manish Chaubey, Tyler G. Rose, Alexa L. Knight, Owen Fick, George P. Lisi & Megan E. Kizer
Department of Chemistry, Brown University, Providence, RI, and Department of Molecular, Cell Biology & Biochemistry Brown University, Providence, RI

Engineering glycan-binding proteins (GBPs) with high affinity and monosaccharide-level specificity remains challenging due to limited understanding of the molecular determinants governing carbohydrate recognition. Here, we present a solution-state NMR investigation of 2.4.i, a directed-evolved Sso7d-based GBP (ssoGBP) that selectively recognizes the Thomsen–Friedenreich (TF) antigen (Galβ1-3GalNAcα-), a tumor-associated carbohydrate expressed in ~80% of cancers. Although prior in silico docking predicted a binding interface dominated by aromatic residues mediating CH-π interactions, our experimental results reveal a distinctly different recognition landscape. 1H–15N HSQC chemical shift perturbation mapping using multivalent TF-PAA identifies a binding interface centered on Y21, R23, D34, and Y42 and neighboring residues rather than the computationally predicted R25, Y28, W30, and Y44. Alanine mutagenesis confirms Y42 as essential for ligand recognition, while W30 primarily contributes to structural stability through cation-π interactions rather than direct carbohydrate engagement. Saturation transfer difference (STD) and DEEP-STD NMR experiments using a stereochemically locked TF ligand demonstrate differential interaction modes across the disaccharide, indicating aromatic-type interactions with the GalNAc N-acetyl methyl group and dispersive aliphatic interactions with the Gal H4 proton. Collectively, these results highlight additional determinants beyond the often emphasized CH-π interactions in carbohydrate recognition and instead support a model in which van der Waals contacts, hydrophobic packing, desolvation, and water-mediated hydrogen-bonding networks cooperatively define specificity.

2026 Poster Abstracts

Briana Mercado

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Investigating redox susceptible residues in the MIF superfamily via mutation

Briana Mercado, Vinnie Widjaja, George Lisi

Brown University

Inflammation is a critical immune response, yet excessive or uncontrolled inflammation contributes to disease progression. Macrophage migration inhibitory factor (MIF) and its homolog, MIF-2, are central mediators of inflammation through activation of the cell surface receptor CD74. Both proteins contain multiple functional motifs, including an evolutionarily conserved proline-1 that confers tautomerase activity and a C-terminal region required for CD74 binding, which can be assayed in vitro and in vivo, respectively. In inflammatory settings, the oxidative cellular environment induces structural and biochemical changes in MIF, giving rise to an oxidized isoform (oxMIF) via modification of cysteine and methionine residues. oxMIF displays reduced catalytic activity but enhanced CD74 binding, making it a promising therapeutic target for antibody-based interventions. However, structural studies of oxMIF are hindered by difficulties in capturing a uniform oxidized population in solution. Remarkably, a single point mutation (Cys80Ala) reproduces key structural and functional features of oxMIF without oxidation. This suggests that targeted mutations can mimic oxMIF-like states. In this poster, I present initial investigations into the role of cysteine and methionine residues in MIF and MIF-2 through loss of function and isosteric substitutions, assessed using a suite of structural and enzymatic assays. The proposed work will help determine whether oxMIF reflects a strictly oxidation-dependent state or a broader conformational state.

Briana Mercado

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Graduate Students of Color in STEM

Briana Mercado, Ells Mine Saint Paul, Lewis Nunez Severino

Brown University

Graduate Students of Color in STEM (GSOCnSTEM) is an SAO recognized graduate student organization. GSOCnSTEM's mission is to build a community of graduate students of color within the STEM disciplines at Brown, increase interaction between faculty and students, and encourage a pipeline for underrepresented groups in STEM within our local community. We do so by hosting events throughout the academic calendar year that focus on social community building and professional development.

Sebastian Millien

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Samuel M. Nabrit Black Graduate Student Association of Brown University

Nabrit BGSA Executive Board

Brown University

The purpose of the Nabrit BGSA is to enhance the intellectual, professional, and social well-being of Black graduate students at Brown University. Nabrit BGSA is designed to meet the social and academic needs of graduate students of African descent; however, membership in Nabrit BGSA is open to any graduate or professional student at Brown University. Nabrit BGSA is a subgroup of the Brown University Graduate Student Council and does not discriminate on the basis of race, ethnicity, gender, age, religion, sexual orientation, national origin, political affiliation, or physical or mental disability. Graduate students can establish membership in Nabrit BGSA through attending any meeting or group event as well as by communicating their desire to be a member to one of the organization's officers. Graduate students can establish membership in Nabrit BGSA through attending any meeting or group event as well as by communicating their desire to be a member to one of the organization's officers.

2026 Poster Abstracts

Camila Molina

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Atomic Details of the FnCRISPR-Cas12a NUC Domain Reveal Allosteric Hotspots Affecting DNA Binding and Cleavage

Camila E. Molina, Anika Weling, Olivia Duarte, and George P. Lisi
Brown University

CRISPR-Cas12a is an RNA-guided endonuclease that is being leveraged as a biochemical tool for genome editing. Target DNA recognition and nuclease-drive cleavage within Cas12a occur at spatially distinct sites, yet their functional coupling suggests an allosteric crosstalk that is reminiscent of the extensively studied CRISPR-Cas9. Cas12a, however, has unique chemistry through the TTTV (V=A, C, G) sequence preference of its protospacer adjacent motif (PAM), ideal for editing T-rich genomes. Cas12a produces staggered cuts of six nucleotide lengths in the target DNA, which are preferable for genome insertions via homology directed repair. This unique DNA cleavage chemistry is controlled by the nuclease lobe of Cas12a, composed of RuvC and an uncharacterized NUC domain. Only RuvC is catalytically active, cleaving both the target and non-target DNA strands. However, mutations in NUC have been shown to attenuate dsDNA cleavage, highlighting its importance to the function of Cas12a. Molecular simulations have shown coordinated structural dynamics between RuvC and NUC throughout the dsDNA cleavage mechanism of Cas12a. This work provides an atomic-level understanding of the functional contribution of NUC and its relationship to RuvC obtained via solution NMR. Preliminary data reveals the potential biophysical characterization of NUC and its fundamental role in understanding the Cas12a DNA mechanism. Results from this project will further optimize CRISPR-Cas12a biology with principles that enhance its genome editing capability.

Michela Oster

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Exocyst undergoes multiple conformational changes to regulate SNARE binding, complex formation, and fusion

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SNARE-mediated vesicle fusion during exocytosis is regulated by the exocyst complex, a multi-subunit hetero-octameric tethering complex. To carry out its functions with exquisite temporal and spatial control, exocyst interacts with a multitude of exocytic factors, including SNAREs, the Sec1/Munc18 (SM) proteins, small Rab and Rho GTPases, PI(4,5)P2 and type V myosin. Exocyst interacts individually with all three exocytic SNAREs, and we show that they exert tight control over several stages of SNARE complex assembly to facilitate membrane fusion. The cryoEM structure of yeast exocyst indicates a compact, fairly static conformation; however, multiple recent studies demonstrate that exocyst undergoes several distinct structural changes involving the Exo70 and Exo84 subunits, which activate the complex for tethering. We also determined that exocyst function is regulated through multiple phosphorylation sites, which affect binding to SNAREs. Other conformational changes are currently being investigated through biochemical and structural studies. We propose that exocyst conformational changes constitute a series of activation steps in order to efficiently tether, bind to SNAREs and accelerate membrane fusion.

Funsho Ogunshola

31

Prolonged Viremia Enhances Cross-Reactivity of HIV-specific T cell Receptors

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Virus-specific CD8+ T cells are crucial in controlling chronic human viral infections such as HIV-1, but the effect of persistent antigen exposure on T cell repertoire formation is not well understood. In this study, we examined epitope-specific CD8+ T cell repertoires in people living with HIV-1, where duration of viremia following hyperacute infection was modulated by the time of initiation of continuous suppressive antiretroviral therapy (ART). After ART-induced suppression of viremia in persons expressing the same HLA class I allele, we analyzed the impact of early (n=6) versus delayed (n=6) ART initiation on the clonotypic composition, cross-reactivity, functional avidity and memory differentiation profile of the HIV-specific T cell repertoire restricted by HLA-B*58:01. Using a panel of barcoded tetramers, we mapped T cell receptor (TCR) clonotypes specific for three dominant epitopes and their variants. Both groups exhibited polyclonal TCR repertoires with evidence of cross-reactivity, which was significantly enriched in donors with prolonged antigen exposure. Within this cohort, broadly cross-reactive clonotypes capable of recognizing all autologous variants were identified, but these were rare (<1%). Early ART initiation preserved repertoires characterized by higher-avidity TCRs and a relative enrichment of transitional memory CD8+ T cell subsets. These functional differences were not associated with differences in TRBV gene sharing, indicating that ART timing shapes repertoire quality and memory differentiation without altering TRBV gene bias. These findings demonstrate how antigen suppression dynamics differentially shape the breadth, functional sensitivity, and memory composition of the HIV-specific TCR repertoire, with implications for T cell-directed immunotherapies and HIV cure strategies.

Anna Nixon

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RNA Polymerase II-dependent Transcription Regulation during Establishment of the Ovarian Reserve

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Brown University

The female ovarian reserve is the finite amount of oocytes established in females during embryonic development and maintained through adulthood. We previously discovered that TATA-box binding protein associated factor 4B (TAF4b) is required for correct establishment of the ovarian reserve. Thus, mice with a disrupted Taf4b gene can be used to study ovarian reserve establishment, maintenance, and the molecular genetic basis of accelerated ovarian aging and female infertility. The transcriptional states of oocytes in the ovarian reserve are dynamic and not well understood, and how RNA polymerase II (RNAPII) provides critical functions to these developing oocytes is unknown. To address these questions, I am investigating the potential role of TAF4b on RNAPII transcriptional regulation in the ovarian reserve. Since TAF4b is a subunit of the Transcription Factor II D (TFIID) complex that recruits RNAPII to initiate transcription, I hypothesize that TAF4b facilitates key transcriptional mechanisms involved in ovarian reserve establishment, and loss of TAF4b drives reduced and delayed transcription. To test my hypothesis, I have examined the presence of RNA polymerase II on meiotic chromosomes between wild-type and Taf4b-deficient oocytes as they are established in the ovarian reserve using standard and super-resolution microscopy. Both TAF4b and RPB1, the largest subunit of RNAPII, are upregulated during meiotic prophase I. More importantly, compared to controls Taf4b-deficient meiocytes show a significant decrease in RNAPII fluorescence intensity. These findings suggest TAF4b is critical for global transcription in the ovarian reserve, and Taf4b-deficiency disrupts oocyte development, a key feature of human infertility.

Zhangshen (Johnson) Li

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Genetic perturbation underlying a novel autosomal recessive intellectual disability syndrome disrupts progenitor mitosis and cortical neurogenesis

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In this study, we investigate the role of a novel gene associated with autosomal recessive intellectual disability (ARID) in brain development. We define the in vivo function of this multifunctional scaffolding protein during neocortical development using a mouse model generated by introducing a patient-derived nonsense mutation. We show that the mutation is a null allele. This mouse model of ARID exhibits neonatal lethality, reduced brain size, and thinning of the cerebral cortex. Histological analyses of neonatal and embryonic brains revealed a marked reduction in neural progenitor populations, accompanied by decreased neuronal density in the developing cortex. These abnormalities arise from defects in cortical progenitor proliferation, including delayed mitotic progression and accumulation of DNA damage, leading to altered cell fate decisions and premature loss of progenitor expansion capacity during early corticogenesis. Together, our findings demonstrate a cellular and neurodevelopmental basis underlying disease-associated brain malformation, providing insights into the pathogenesis of ARID.

Yovany Padilla Jr

34

Investigating the Therapeutic Potential of TMZ and BIA on the DNA Damage Response

Yovany Padilla Jr, Phlippa V Beaucaire, Noe Mercado, Sean E. Lawler
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Identification of approaches to improve the efficacy of standard of care therapy would be useful in the treatment of glioblastoma (GBM). Alterations in the DNA damage response (DDR) pathways enable tumor cells to resist DNA-damaging therapies including temozolomide and irradiation (TMZ/IR). Additionally, glioma stem cells have demonstrated increased resistance to chemoradiotherapy due to their enhanced activation of DDR pathways.

The indirubin-derivative 6 bromo-indirubin-acetoxime (BIA) is a brain penetrant small molecule that has shown efficacy as a single agent in GBM mouse models, where it has effects on tumor angiogenesis and GBM cell invasion. BIA acts as a broadly selective protein kinase inhibitor. In this study we investigated the combination of BIA with TMZ in GBM cells and its effects on the DDR activated protein kinase CHK1, which is activated in response to DNA damage leading to DNA repair and TMZ resistance.

Analysis of kinase inhibitor databases indicated that indirubin derivatives inhibit CHK1 protein kinase in vitro with an IC50 in the 100-500 nM range. We evaluated effects of BIA and TMZ in a panel of GBM cells using cell viability assays and DNA damage was assessed by γH2AX phosphorylation. CHK1 phosphorylation was measured by Western blotting.

BIA treatment at a concentration of 1 mM for 72 hours had no effect on GBM cell viability but significantly enhanced cell killing by TMZ in all cell lines tested. This was associated with increased levels of DNA damage as measured by levels of γH2AX phosphorylation. Mechanistic analysis revealed a corresponding decrease in both CHK1 and pCHK1 levels in patient-derived G9 GBM cells, Overall, the combination of BIA and TMZ showed promising results in across patient-derived GBM stem cell models and cell lines, and our data suggest a role of CHK1 inhibition in mediating these effects. These data support further exploration of BIA as a potential therapeutic agent for GBM therapy.

Yanixa Quiñones Avilés

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Baseline cellular state dictates the molecular impact of KRAS mutant variants in pancreatic cancer cells

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KRAS is mutated in over 90% of pancreatic ductal adenocarcinomas (PDAC), where hotspot alterations in codons 12, 13, and 61 drive tumor initiation and progression. Although distinct biochemical properties have been described for individual KRAS mutants, whether they generate unique allele-specific signaling programs in PDAC cells remains unresolved. Here, we systematically interrogated the molecular consequences of seven common KRAS mutant variants in reconstituted isogenic, KRAS-deficient PDAC cell lines by integrated transcriptomic, proteomic, and phosphoproteomic profiling. We found that baseline cellular state, rather than allele identity, was the predominant driver of molecular variation. Comparisons with established KRAS reference signatures revealed significant but moderate overlap at the mRNA level and less so at the proteome level. Pathway analyses highlighted interferon response and mitochondrial translation as recurrently altered across alleles, while phosphoproteomic data confirmed robust ERK1/2 activity and suppression of DYRK kinase substrates by mutant KRAS expression. Importantly, no robust allele-specific molecular programs were identified. Together, our study establishes a comprehensive multi-omics resource for KRAS signaling in PDAC and demonstrates that cellular context exerts a stronger influence than allele identity in shaping molecular profiles, with implications for interpreting putative allele-specific signaling dependencies and therapeutic vulnerabilities.

Caleb Schultz

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Characterizing the Beta-Amyloid Microenvironment in Alzheimer's Disease with Spatial Transcriptomics

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In recent years, spatial transcriptomics research of Alzheimer's disease has progressed our under- standing of cellular and molecular changes in the amyloid-beta (ABeta) microenvironment. However, these studies largely rely on discrete spatial binning practices that are not biologically informed, limiting our knowledge of local mechanistic progression of the disease cascade. This thesis examines the continuous molecular gradient surrounding ABeta plaques in human tissue and utilizes it to define interpretable, data-driven zone boundaries using Visium-SPG data from Kwon et al. (2023), incor- porating both minimum-plaque distance and cumulative ABeta exposure metrics. We find that key cellular and molecular programs, including astrocyte activation, oligodendrocyte disruption, neu- ronal/synaptic loss, and mitochondrial dysfunction, show distinct, spatially-dependent expression gradients. By investigating activation threshold distances across gene modules, cell states, and cell communications, we infer a spatially ordered cascade of microenvironment changes. We find these patterns persist after controlling for cortical depth and are robust across multiple modeling choices, which supports the approach of gradient-based spatial methods. Together, this work evaluates the ABeta microenvironment as a continuous and partially ordered system, thereby providing a framework for connecting spatial organization with disease mechanisms in human Alzheimer's tissue.

Emma Sedivy

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S-acylation of a hyper-thermophilic bacteriophage is essential for infection

Emma Sedivy, John Haley, Sy Redding, Brian Kelch
University of Massachusetts Medical School

All viruses must recognize and gain entry to their hosts. To better understand the biochemical and structural features that enable a virus to infect its host, I examined a bacteriophage that does so in an extremely harsh environment. Bacteriophages (phages) are viruses that infect and kill specific strains of bacteria and show great potential as biocontrol agents. To fully realize this power, it will be necessary to engineer phages that can withstand environmental stresses and specifically target bacteria with high potency. The phage Oshimavirus was isolated from geothermal hot springs at 65-75˚C where the hot temperature and the low concentration of hosts make recognition difficult. Thus, Oshimavirus faces challenges like those faced by all viruses, but on an intense scale. I determined structures of the Oshimavirus infection apparatus and examined them for adaptations that would aid host recognition in adverse conditions. Surprisingly, a key component of the host-recognition complex is S-acylated with a long, unsaturated fatty acid. Interestingly, this modification is not required for attachment to the host, but is essential for subsequent steps of infection. S-acylation of proteins has not previously been observed on phages. Furthermore, modification with this fatty acid moiety has not been observed before in any proteins. In ongoing work, I am investigating the bacteriophage's structure after S-acylation has been chemically removed to determine how this novel post-translational modification enables infection. A detailed understanding of this fascinating thermophage will broaden our understanding of viral infection mechanisms and the possibilities of biology in extreme environments, enabling future bioengineering efforts.

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