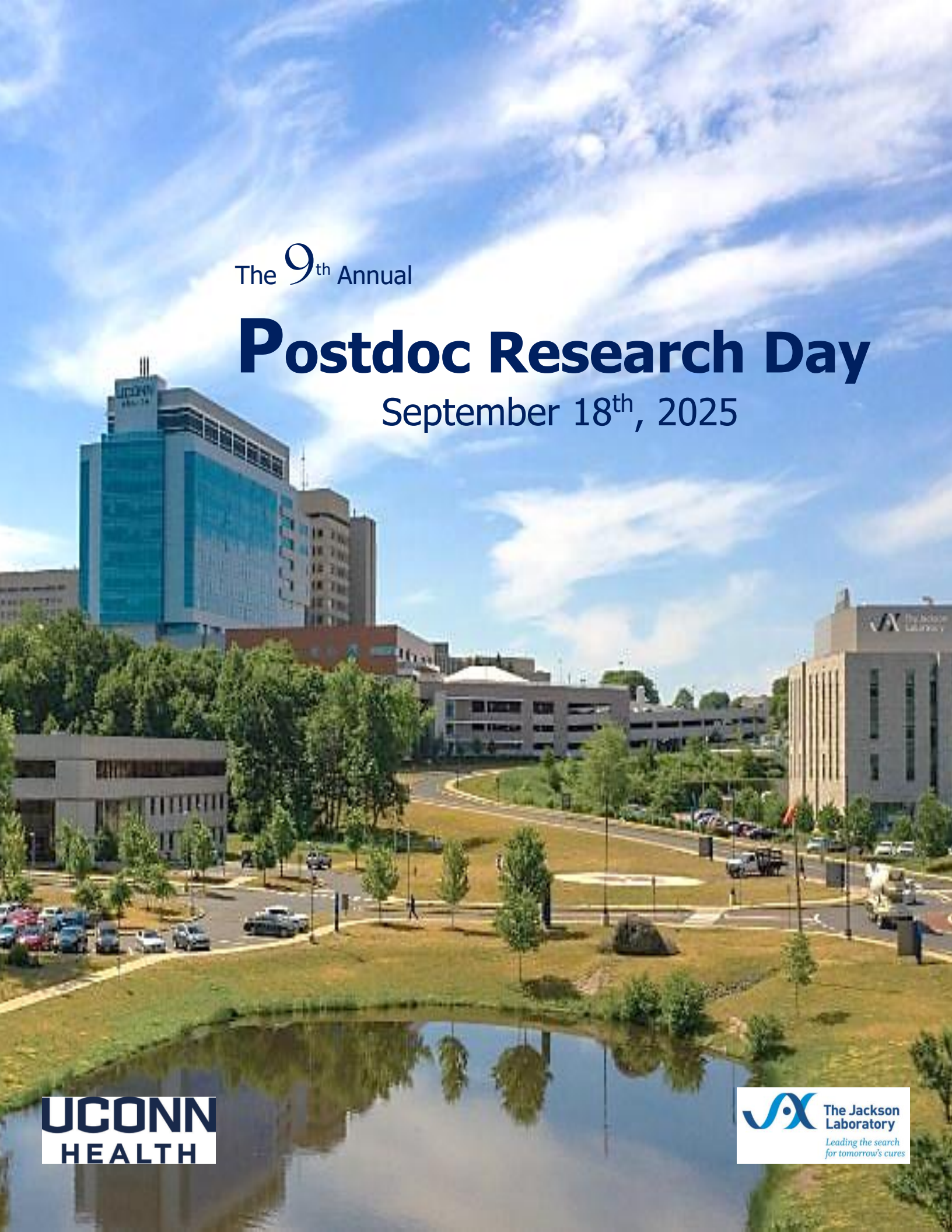

The 9th Annual

Postdoc Research Day

September 18th, 2025

UCONN HEALTH

The Jackson Laboratory
Leading the search for tomorrow's cures

Welcome to the ninth annual UConn Health/Jackson Laboratory Postdoc Research Day. As part of National Postdoc Appreciation Week, this event is a chance for us to celebrate our postdocs and the important work they are doing here at UConn Health and the Jackson Laboratory for Genomic Medicine. Thank you to everyone for coming out to support and acknowledge these postdocs. Today, we will showcase some of the important work they are performing through a series of short Speak4Science talks and a full poster session. We also have an exciting keynote address from Dr. Nenad Sestan from Yale University. On the following pages, you will find a schedule as well as abstracts for all our presenters.

I would like to thank the Health Center Research Advisory Council for their support of this year's event as well as Jane Tran Sills for all her help in putting this together. I would also like to thank our PDRD Planning Committee:

Tomi Faniyan (UConn Health)
Katarina Milicevic (UConn Health)
Patience Shumba (UConn Health)
John Stout (UConn Health)
Luke Trinity (Jackson Labs)

Be well,

Christopher D. Heinen, Ph.D.
Director of Postdoctoral Affairs
UConn Health

The 9th

Postdoc Research Day

Thursday, September 18th, 2025

1:00	**Opening Remarks**	**Academic Rotunda**
1:05	**Speak4Science Part I**	**Academic Rotunda**
1:50	**Coffee Break**	**Rotunda Lobby**
2:20	**Speak4Science Part II**	**Academic Rotunda**
3:15	**Keynote Address:**	**Academic Rotunda**

Nenad Sestan, M.D./Ph.D.

Harvey and Kate Cushing Professor of Neuroscience,

Professor of Comparative Medicine, Genetics and

Psychiatry

Yale University School of Medicine

TBD

4:30	**Poster Session and Reception**	**Rotunda Lobby**
4:40	**Poster Presentations I (Odd numbers)**	**Rotunda Lobby**
5:20	**Poster Presentations II (Even numbers)**	**Rotunda Lobby**
6:00	**End**	

Our Speak4Science event will feature a series of 4-minute talks by our postdocs. Each speaker will use one slide to broadly introduce their area of research and why it excites them. To learn more about the details of their research, I encourage you to visit the poster sessions starting at 4:30 PM. The speaker roster and their corresponding poster numbers are listed below.

Name	Title	Affiliation	Poster
1. John Stout	*Signal control by layer 6 corticothalamic neurons*	UCH	12
2. Katarina Milicevic	*Neurophysiological changes in the App$^{NLGF/-}$ model of AD*	UCH	13
3. Emily Burrage	*ATP13A3 and endothelial cells integrity*	UCH	14
4. Anirudhya Lahiri	*Peripheral demyelination in GLD*	UCH	15
5. Sanjeev Yadav	*Anti-miRs: A new frontier in stroke care*	UCH	16
6. Ali Zelan	*Social validity assessment in early childhood intervention*	UCH	25
7. Emilie Butler	*MAPP preliminary outcomes of a pilot RCT*	UCH	26
8. Bridget Hayes	*Functional impairment in SUD remission*	UCH	27
9. Yurui Zheng	*Dual pathway modulation by 4-HPAA*	UCH	28
10. Rajkishor Pandey	*CDH17-targeted CART cells for PDAC treatment*	UCH	5
11. Nisha Mahey	*Damage repair in* S. aureus *persisters*	UCH	3
12. Maeva Devoucoux	*Splicing control of EZH2 in TNBC*	JAX	17
13. Tasnif Rahman	*Multiscale models of the gut-microbiome*	UCH	2
14. Wenqiang Du	*Piezo1 links scar inflammation to PAS*	UCH	21
15. Corie Owen	*Interfollicular communication in ovaries*	UCH	23
16. Caroline Haney	*Endometriosis spatial transcriptomics*	JAX	22
17. Xuan Ye	*snoRNAs and 2'-O-methylation in Drosophila*	UCH	19
18. Luke Trinity	*Prediction of CMV status via scRNA-seq*	JAX	18
19. Govindaraj Perumal	*Senolytic drug delivery to aged bone repair*	UCH	11
20. Su Xu	*Harmonizing ST data across slices*	UCH	20
21. Naushad Khan	*Engineered NK cells to fight HIV*	JAX	29

Keynote Presentation

Nenad Sestan, M.D./Ph.D.

Info coming soon

Abstracts

1. Kavitha Kannan

Examining the mechanisms of beneficial effects of *Indy* reduction on fly gut physiology
Kavitha Kannan[1], Kali Meadows, Dushyant Mishra, Jacob Macro, Nagham Khouri Farah, Ryan Rogers and Blanka Rogina[1].

[1]Genetics and Genome Sciences Department, UConn Health

The *Indy* (I'm not dead yet) gene encodes a transporter of tricarboxylic acid (TCA) cycle intermediates with highest affinity for transporting citrate. INDY reduction in fruit flies and worms affects metabolism and extends lifespan. In *Drosophila*, INDY is expressed in metabolic tissues such as the midgut, fat body and oenocytes. *Indy* reduction mimics beneficial effects of calorie restriction on metabolism and aging. One of the beneficial effects of *Indy* reduction on fly health, is preservation of intestinal stem cell (ISC) homeostasis and midgut integrity by affecting intermediary metabolism, reducing oxidative damage and increasing mitochondrial biogenesis. The emerging role of midgut in healthy aging led us to investigate how INDY reduction in fly intestine influences nutrient signaling and tissue homeostasis. Here we sought to investigate mechanism of effects of reduced INDY levels on ISC homeostasis in the midgut under different dietary conditions using transcriptomic approaches. Our bulk RNAseq data show that *Indy* flies in response to a high calorie diet display upregulation of biological processes involved in lipid catabolic process, cytoplasmic translation and detoxification while processes such as protein maturation, protein folding and Golgi vesicle transport are downregulated relative to control flies on high calorie diet. The scRNAseq data show that *Indy* flies exhibit differences in relative abundance of midgut cell types in response to both standard and high calorie diet in young female flies compared to control flies on the respective diets. In comparison to control flies under high calorie conditions, *Indy* flies display a low proportion of entero-endocrine (EE) cells that secrete hormones and mediate cross-talk between the gut and other tissues. Taken together, our data highlight the effects of INDY reduction in different midgut cell types that contribute to fly health and longevity.

2. Tasnif Rahman

Towards Multi-Scale Models of Gut Microbiome-Host Interactions using the Vivarium Interface
Tasnif Rahman[1], Edwin Moses Appiah[1], Ryan Spangler[1], Eran Agmon[1]

[1]Center for Cell Analysis and Modeling, UConn Health

Background The gut microbiome has strong bidirectional interactions with the host-intestinal tissue that regulate both the microbial community dynamics and intestinal cell turnover and differentiation. Studying such multifaceted and complex interactions is challenging, and thus truly multiscale models are required to help interpret the increasing volume of *in vivo* data. Therefore, we suggest using the Vivarium integrative modeling platform to develop a multiscale, spatial model connecting microbiome community metabolism to the tissue dynamics of the intestinal crypts.
Methods We used the Vivarium 2.0 interface to first develop a bacterial community metabolism model. The metabolic dynamics of individual species of bacterial are simulated using the dynamic Flux Balance Analysis (dFBA) method, wherein concentrations of metabolites in an external environment are used to constrain exchange reactions of those metabolites. Each dFBA is created as a Vivarium "process" which can represent individual species or strains of bacteria, these can then be connected through an external environment to create a community dFBA (cdFBA) model where all species share the same external metabolite source. We then used Vivarium's multiscale integration ability to connect cdFBAs spatial grid, allowing diffusion and

advection of metabolites and bacterial biomass in space-using a finite-volume approach. This allows for spatial simulations of dynamic aspects of the gut environment – such as peristalsis.
Results We were successfully able to develop a cdFBA model which uses parallel dFBA's to simulate a community of bacteria. We were able to recapitulate conceptual aspects of bacterial community dynamics such as cross-feeding, diauxic shifts, and resource competition. Similarly, we were also able to demonstrate diffusion and advection of metabolites in spatial cdFBA simulations – mimicking peristalsis like advection.

3. Nisha Mahey

Post-fluoroquinolone treatment molecular events and nutrient availability modulate *Staphylococcus aureus* antibiotic persistence

Nisha Mahey, PhD[1#], Jonathan I. Batchelder[1#], Wendy W. K. Mok, PhD[1]

[1]Department of Molecular Biology & Biophysics, UConn Health
[#]Contributed equally

Staphylococcus aureus is a bacterial pathogen associated with about one million deaths per year. *S. aureus* infects many host sites, including skin and the airway. At nutrient-limited infection sites, competition with immune cells can further deprive *S. aureus* of metabolites, forcing the bacteria to enter a state of reduced metabolic activity. While lower metabolic activity may help contain the growth of the pathogen, it can also enhance *S. aureus*'s survival during antibiotic treatment. Here, we focus on *S. aureus*'s response to fluoroquinolones (FQs), which inhibit topoisomerases necessary for nucleic acid synthesis and can lead to double-stranded DNA break (DSB) formation. We show that even in the stationary phase, when nucleic acid synthesis levels are minimal, loss of DNA repair enzymes reduces *S. aureus*'s FQ persistence. Using genetic and imaging approaches, we found that both persisters and cells that die induce DNA damage responses after FQ treatment terminates, and DNA repair enzymes are needed mainly during this recovery period. We found that starving *S. aureus* after treatment significantly increases FQ persistence, even in cells lacking the ability to repair DSBs. Our data suggest that starvation increases persistence by delaying the resumption of nucleic acid synthesis after treatment, allowing time for FQs to dissociate from trapped topoisomerases and be expelled from the cell. This study demonstrates that the nutritional environment and molecular events during post-FQ recovery are crucial in determining the survival of *S. aureus*. Our findings point to processes that can be targeted to sensitize *S. aureus* to FQs to improve treatment outcomes.

4. Ashok Kumar Dhinakaran

Microneedle patch technology for integrated skin immune–microbiota profiling across aging and infection

Ashok Kumar Dhinakaran[1], Morgan Severn[4], Anita Y Voigt[1,4], Soo Yeon Kang[1], Julia Oh[4], Sasan Jalili[1,2,3]

[1]The Jackson Laboratory for Genomic Medicine
[2]Department of Immunology, School of Medicine, University of Connecticut
[3]Department of Biomedical Engineering, University of Connecticut
[4]Department of Dermatology, Duke University, Durham, NC

The skin is a critical interface for host–microbe interactions yet capturing both immune and microbial components simultaneously has been challenging with traditional biopsy-based methods. Here, we introduce a novel microneedle patch (MNP) platform that enables minimally invasive, longitudinal sampling of skin-resident immune cells, cytokines, and microbiota. We optimized patch design and collection protocols to ensure robust recovery of viable immune cells and microbial populations, demonstrating successful dual sampling of both commensal and pathogenic microbiota from animal and human skin. Validation using a *Staphylococcus aureus* infection model in C57BL/6 mice, confirmed that MNPs can simultaneously capture

dynamic immune responses and microbiome composition. Bulk RNA-Seq of infected tissue revealed largely conserved transcriptional responses across age groups, with gene expression differences driven primarily by infection rather than age. However, MNP-based sampling of interstitial fluid uncovered subtler immunological changes not captured by bulk tissue analysis. Young mice displayed robust T cell recruitment in both single time-point and longitudinal analyses, whereas this response was markedly attenuated in old mice. These findings underscore the utility of MNPs to reveal nuanced age-related differences in skin immunity that may underlie increased susceptibility to infection in aging. Building on these findings, we are now examining whether variation in tissue-resident memory and regulatory T cell abundance and function contributes to infection outcomes. By enabling paired, longitudinal sampling of the skin immune cells and microbiota, our MNP technology provides a powerful tool to dissect host–microbiome–immune interactions across aging, infection, and commensal-driven protection. This platform has broad potential to advance understanding of skin health and resistance to infection.

5. Rajkishor Pandey

Development of CDH17-targeted CAR-T cells for pancreatic adenocarcinoma treatment

Rajkishor Pandey[1], Kevin Staveley-O'Carroll[1], Eric T Kimchi[1], Guangfu Li[1,2]

[1]Department of Surgery, University of Connecticut Health Center,
[2]Department of Immunology, University of Connecticut Health Center

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of carcinoma in the human pancreas (more than 95 % cases). Pancreatic cancer diagnosis in the early stage is challenging due to its asymptomatic where the chance of curing is greatest. In normal cells, cell adhesion molecule cadherins help to maintain cell structure and functions appropriately. Candherin-17 (CDH-17) is one of the cadherin family surface proteins proficiently expressed in pancreatic tumor tissue and helps with tumor progression in the pancreas and other organs. Therefore, CDH-17 might be used as an immunotherapeutic target antigen against PDAC. At present study, the significant overexpression of CDH-17 was detected in different human & mouse tumor cell lines & human PDAC patients than normal peritumor tissue. Therefore, the single-chain variable monoclonal antibody domain of CDH-17 antigen has been designed as a chimeric antigen receptor (CAR) in the lentivirus (LV) backbone. The designed and synthesized CDH17-CAR was transducted into jurkat T cells with the addition of polybrene (8 µg/mL). Around 90 % of CAR-mCherry expressions on the surface of jurkat T cells were detected by flowcytometry. Furthermore, CAR-T has shown significant binding specificity with human and mouse PDAC cell lines on CDH-17-expresstion basis. Apart from binding specificity, CAR-T cells showed significant cytotoxicity to different human PDAC cell lines based on CDH17 expression with the release of proinflammatory cytokines. Additionally, CAR-T cells showed higher proinflammatory cytokines expression when co-cultured with human patient derived organoid. Further, need to validate CAR-T (jurkat) cells as well as primary human PBMC derived CAR-T antitumor effects in the patient derived organoid model (PDOM) and NSG mice xenograft model.

6. Fahrin Patel

Mincle—The Immune Alarm Amplifying Metabolic dysfunction-associated Steatohepatitis (MASH)

Farhin Patel[1], Colin Varnet[1], and Adam Kim[1]

[1]Department of Gastroenterology, UConn Health

The prevalence of MASH has increased radically, currently affecting 5% of the U.S. adult population. MASH is a progressive liver disease that is linked to obesity and metabolic syndrome, where excessive accumulation of fat in the liver leads to inflammation and fibrosis. Patients with MASH have an increased risk for severe infections, likely due to dysfunctional immune responses. Mincle, a C-type lectin receptor, recognizes

damage-associated molecular patterns (DAMPs) and contributes to immune cell infiltration and tissue injury in MASH. Mincle knockout (MKO) mice are protected from liver injury caused by a high-fat diet, making Mincle a potential therapeutic target. However, our group observed that MKO mice exhibit worsened adipose tissue inflammation following acute stimulation with bacterial lipopolysaccharides (LPS). We hypothesize that Mincle is an essential immune regulator in the liver and adipose tissue during MASH and in response to infection. To model MASH, 5-week-old C57BL/6 and MKO mice were fed with a fat-, fructose, and cholesterol-rich (FFC) diet or standard chow for 12 weeks. Mice were administered LPS (0.7 mg/kg) or saline intraperitoneally 24 hr before euthanizing as a model of acute bacterial infection during MASH. At the end of the experiment, metabolic activity was assessed using the Comprehensive Lab Animal Monitoring System (CLAMS). MKO-FFC-LPS mice depicted reduced liver weight, liver-to-body weight ratio, and triglyceride levels compared to the WT-FFC-LPS group. Both liver and adipose tissue had reduced inflammatory markers in the MKO FFC-LPS group. In adipose tissue, the MKO-FFC-LPS group showed downregulated levels of Ly6G and adipokines such as leptin and resistin transcripts, while adiponectin was upregulated compared to the WT-FFC-LPS group. CLAMS data revealed that MKO mice consumed less FFC diet but had similar energy expenditure. Upon LPS challenge, MKO-FFC-LPS mice ate more than WT-FFC-LPS mice, indicating a more robust response to infection. Targeting Mincle could be a strategic preventative approach for attenuating inflammation in MASH.

7. Moriah Turcotte

Perinuclear β-adrenergic receptors are necessary and sufficient to promote cardiac hypertrophy

Moriah Turcotte Ph.D.[1], Anne-Maj Samuelsson Ph.D.[2], Sofia M. Possidento M.S.[1], Jinliang Li Ph.D.[2], Zhuyun Qin Ph.D.[2], Michael Kapiloff M.D., Ph.D.[2], Kimberly Dodge-Kafka Ph.D.[1]

[1]Calhoun Center for Cardiology, Department of Cell Biology, UCONN Health
[2]Department of Ophthalmology and Medicine, Stanford Cardiovascular Institute, Stanford University, Stanford, CA

Pathological cardiac hypertrophy development is controlled by networks of signaling pathways, integrated by scaffold proteins that localize signaling enzymes and facilitate crosstalk between these pathways, leading to upregulation of hypertrophic transcription factors. Over the last several decades, our lab has studied a protein scaffold at the nuclear envelope, muscle A-Kinase Anchoring Protein (mAKAPβ), required for the induction of cardiac hypertrophy. Among the various pathways affected, mAKAPβ particularly tethers downstream targets of β-adrenergic receptors (βAR), and this localization provides the framework for stress-related gene transcription in cardiomyocytes. Although the traditional dogma of adrenergic receptor signaling posits receptor activation begins at the plasma membrane, recent evidence has emerged showing intracellular adrenergic receptor localization and activation. We now provide evidence of a perinuclear cAMP domain that is less than 25nm in size, dependent on mAKAP expression and localization of PDE4D3 and th RII subunits of PKA. Utilizing novel peptides localized to mAKAP, we stimulated or inhibited perinuclear βARs within proximity. We demonstrate perinuclear βARs, likely expressed on the Golgi apparatus, are necessary and sufficient for cardiac hypertrophy development in neonatal and adult rat cardiac myocytes, constituting a functionally independent cAMP domain. This research has high therapeutic value as our peptides prevent disease without impacting canonical cardiomyocyte function.

8. Mingchong Yang

The integrated stress response suppresses PINK1-dependent mitophagy by preserving mitochondrial import efficiency

Mingchong Yang[1#], Zengshuo Mo[1#], Kelly Walsh[1], Wen Liu[2], Xiaoyan Guo[1]*

[1]Department of Genetics and Genome Sciences, University of Connecticut Health Center
[2]Department of Molecular Biology and Biophysics, University of Connecticut Health Center
[#] Authors contributed equally.

Mitophagy is crucial for maintaining mitochondrial health, but how its levels adjust to different stress conditions remains unclear. In this study, we investigated the role of the DELE1-HRI axis of integrated stress response (ISR) in regulating mitophagy, a key mitochondrial quality control mechanism. Our findings show that the ISR suppresses PINK1-dependent mitophagy under many mitochondrial stress conditions by positively regulating mitochondrial presequence protein import, independent of ATF4 activation. Mitochondrial presequence protein import is regulated by the rate of protein synthesis. Without ISR, increased protein synthesis overwhelms the mitochondrial import machinery, reducing its efficiency. Under severe depolarizing stress, mitochondrial import is heavily impaired even with active ISR, leading to significant PINK1 accumulation. In contrast, mild mitochondrial stress allows more efficient protein import in the presence of ISR, resulting in lower mitophagy. Without ISR, mitochondrial protein import becomes severely compromised, causing PINK1 accumulation to reach the threshold level necessary to trigger mitophagy. These findings reveal a novel link between ISR-regulated protein synthesis, mitochondrial protein import, and mitophagy, offering potential therapeutic targets for diseases associated with mitochondrial dysfunction.

9. Arnab Mutsuddy

Simulating Microbial Systems – A platform for scalable and accessible multiscale whole cell simulations and analysis

Arnab Mutsuddy[1], Alexander A. Patrie[1], Sean Y. Cheah[3], James C. Schaff[1], Ryan K. Spangler[1], Suzanne Paley[2], Markus Krummenacker[2], Peter D. Karp[2], Markus W. Covert[3], Eran Agmon[1]

[1]Center for Cell Analysis and Modeling, UConn Health
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[3]Department of Bioengineering, Stanford University, Stanford, California, USA

The *E. coli* whole-cell model represents a landmark achievement in systems biology, capable of simulating a wide range of biological phenotypes across diverse environmental conditions. Its architecture integrates multiple function-specific submodels built on diverse mathematical formalisms, requiring complex software and specialized expertise for execution, analysis, and validation. As part of the DARPA-SMS (Simulating Microbial Systems) program, our group is developing an accessible computational infrastructure to support multiscale mechanistic simulations of *E. coli* at single-cell resolution. The overarching objective is to develop, parameterize, and experimentally validate predictive models of *E. coli* with applications in biomanufacturing (e.g., Violacein production) and antibiotic response prediction (e.g., Mecillinam). Within this effort, our group focuses on creating a generalizable and extensible simulation platform that integrates heterogeneous subsystem models into the whole-cell framework. Building on our prior development of Vivarium, a hybrid modeling framework, we are designing a scalable platform deployable across high-performance computing environments as well as local workstations. The infrastructure will support generation of high-resolution outputs at molecular, cellular, and population scales, enabling detailed mechanistic simulations of gene expression, protein–protein interactions, and metabolite dynamics. In addition, streamlined data integration and advanced visualization tools will facilitate interpretation of complex simulation results. Together, this work advances the accessibility and applicability of whole-cell modeling, enabling predictive simulations that bridge experimental and computational microbiology.

10. Nagaraju Marka

Senolytic cocktail dasatinib and quercetin impaired influenza- induced muscle wasting in aged mice
M. Nagaraju, Andreia N. Cadar, Zena L Haddad, Anchala Anil Rao, Rakshit Raj, Erica Lorenzo, Laura Haynes, Jenna M. Bartley

UConn Center on Aging, University of Connecticut School of Medicine
Department of Immunology, University of Connecticut School of Medicine

Influenza (flu) remains a major burden for older populations with increased morbidity and mortality. In older people, flu infection can lead to loss of physical function. In preclinical murine studies, the Bartley lab previously determined that flu leads to functional decline, muscle-localized inflammation, and muscle degradation and atrophy; and that these effects are exaggerated and prolonged with aging. Cellular senescence accumulate with aging and leads to excessive inflammation via the senescent-associated secretory phenotype (SASP). Treatment with senolytics, dasatinib and quercetin (D+Q), eliminates senescent cells and improves the health span, metabolic functions, reduces muscle inflammation and promotes satellite cell proliferation in aging animal models. Hence, we aimed to determine if pretreatment with D+Q could protect against flu-induced muscle declines in aging. Aged (18-20M) C57BL6/J male and female mice were treated with D+Q prior to sublethal flu infection. Immune responses, physical function, and skeletal muscle parameters were assessed prior to and following flu challenge. D+Q did not impact flu-induced weight loss, lung viral load, and flu-specific CD4 and CD8 T cells responses in the mediastinal lymph node and spleen. However, D+Q treatment mitigated flu-induced functional declines in both male and female with increased grip strength compared to vehicle control. In male D+Q treatment led to reduced gene expression of muscle atrophy markers Atrogin-1 and MuRF-1 compared to vehicle treated mice at 11- days post-infection. In totality, our results suggest senolytics may protect against flu-induced muscular declines without impacting immune responses in aged mice, which may offer insights for potential therapeutic implications.

11. Govindaraj Perumal

Optimizing Senolytic Drug Delivery Timing to Enhance Aged Bone Repair
Govindaraj Perumal Ph.D., Travis Robert Wallace, Liisa Kuhn Ph.D.

Department of Biomedical Engineering, School of Dental Medicine, UConn Health

Bone repair is challenging for aged women due to several factors, including a lower bone mineral density and cellular dysfunction of immune cells, osteoprogenitors, and osteoclasts. The normal balance of osteoblast and osteoclast activity is affected by the combination of cellular dysfunction, chronic inflammation, and accumulation of senescent cells (SCs) that occur with aging. Previous studies have shown that the targeted elimination of SCs has beneficial effects on bone density in old mice. Recently, other studies have shown that short, repeated doses of senolytic drugs improve bone healing in aged mice. Bone grafts and bone graft substitutes are used to assist with the healing of bone injuries or implant fixation. Given the off-target effects of senolytics on the normal function of immune cells that are actively participating in bone repair during the first week after injury, we utilize bone coatings on bone graft substitutes for localized delivery of senolytics. We hypothesize that calcium phosphate coatings on bone graft substitutes can be used to optimize the delivery timing of ABT-263, a senolytic, to improve bone healing. We tested the effects of early (immediate) and late (after 7 days) delivery of the senolytic drug ABT-263. The timing effect of ABT-263 drug delivery was evaluated in vitro with chemically aged MC3T3-E1 mouse osteoprogenitor cells and in vivo calvarial bone defect studies in aged mice >20 months old. In vitro outcomes studied included measuring the reduction of senescent cells, in vitro mineralization, and assessing key osteogenic and inflammatory genes. In vivo bone regeneration was assessed by micro-CT analysis, immunohistochemistry, and histological studies (bone labels, ALP, TRAP). Interestingly, the in vitro studies proved that delayed delivery of ABT-263 significantly improved mineralization and reduced osteoclastogenesis rather than immediate delivery. Analysis is ongoing

of the recently retrieved 9-week time point samples from the in vivo calvarial defect studies in old mice. Our data thus far indicates that delayed delivery of the senolytic ABT-263 may be the optimal profile to enhance osteogenesis and bone repair.

12. John Stout

Local Signal Control by Prefrontal Layer 6 Corticothalamic Neurons

John Stout[1] and Timothy Spellman[1]

[1]Department of Neuroscience, UConn Health

Prefrontal corticothalamic loops are fundamental to executive function but remain poorly characterized. In the visual cortex, layer 6 corticothalamic neurons (L6CT) contact local interneurons to control the response amplitude, but not neuronal representations of layers 2/3 and 5 neurons. We hypothesized that prefrontal L6CT neurons served a similar gain-modulating purpose; to control signal amplitude while maintaining representations for executive function of local neuronal populations. To test this idea, we combined two-photon calcium imaging of the prefrontal cortex with optogenetic manipulation of L6CT neurons as mice performed a head-fixed cognitive flexibility task. Optogenetic pacing of L6CT neurons was timed to trial feedback epochs and intertrial-intervals of a cognitive flexibility task that demanded selective attention to one modality (e.g. olfaction) while ignoring another (e.g. whisker-vibratory stimuli). By aligning red-light illumination to interframe periods through an implanted microprism, we photoactivated L6CT neurons expressing ChrimsonR+ while recording 605 prefrontal neurons expressing Syn-GCaMP6f across 6 mice. L6CT photoactivation excited 11% while suppressing 25% of neighboring neurons. Using a generalized-linear model, we found that L6CT activation broadly disrupted task representation, even amongst neurons not directly photomodulated. During light-off trials, suppressed neurons more strongly represented trial-outcome (correct vs error) relative to excited neurons. In contrast, during light-on trials, the representations of most excited neurons were gain-modulated. These results indicate that prefrontal L6CT neurons serve to control local cortical computations by selectively amplifying the task representation of a key group of neurons while broadly disrupting higher-order task representation amongst non-activated neurons.

13. Katarina Milicevic

Passive and active membrane properties in the heterozygous App$^{NLGF/-}$ model of Alzheimer's disease

Katarina D. Milicevic[1,2], Yan M.D. Zhu[1], Violetta O. Ivanova[1], Riqiang Yan[1], and Srdjan D. Antic[1,2]

[1]Neuroscience Department, University of Connecticut School of Medicine
[2]Institute for the Brain and Cognitive Science, University of Connecticut

The heterozygous App$^{NLGF/-}$ mouse model of Alzheimer's disease (AD) replicates key aspects of human pathology, including late-onset amyloidosis and mild cognitive and histological changes, making it more representative of the human condition compared to the homozygous model. Here, we performed electrophysiological and metabolomic analysis of heterozygous App$^{NLGF/-}$ mice in young (<100 days) and old (>200 days) cohorts. Physiological assessments using whole-cell recording revealed that, compared to healthy littermates, heterozygous NLGF mice exhibited higher input resistance, increased h-current, and enhanced input/output potential firing. In the young group, void of plaques, whole cell recordings showed heightened frequency of spontaneous excitatory postsynaptic currents (sEPSCs) and increased epileptiform activity in response to a K+ channel blocker, 4-aminopyridine, which was attenuated by the gap junction blocker carbenoxolone (more effectively in App$^{NLGF/-}$ mice) suggesting a role for enhanced gap junctional coupling in network dysfunction. Using NMR spectrometry, we assessed the metabolome of whole brain lysates, however, no consistent genotype-dependent changes in neurotransmitter or amino acid levels were found, indicating that regional alterations may be masked in bulk tissue analysis. These findings provide the

first integrated electrophysiological and metabolomic characterization of heterozygous $App^{NLGF/-}$ mice, highlighting key features of AD-associated neurophysiological changes.

14. Emily Burrage

ATP13A3 is important for brain endothelial cell integrity and putrescine uptake
Emily Burrage[1], Ashok Cheemala[1], Patrick Murphy[1]

[1]Vascular Biology, UConn Health

Amyotrophic Lateral Sclerosis (ALS), Frontotemporal Dementia (FTD), and Alzheimer's Disease (AD) are devastating neurodegenerative disorders with 97% of ALS, 50% of FTD, and 50% of AD cases characterized by cytoplasmic aggregation and loss of nuclear function of the RNA-binding protein TDP-43. Evidence from our lab showed reduced TDP-43 in the capillary endothelium in the cerebral cortex of donors with ALS/FTD and AD. Modeling this loss in mice revealed disruptions in endothelial cell (EC) and blood-brain barrier (BBB) integrity. TDP-43 plays a critical role in RNA splicing, and the most strongly perturbed splicing event in our mouse models was ATP13A3, a putrescine transporter. Putrescine, a polyamine, is tightly regulated through synthesis, uptake, and degradation and dysfunction of polyamine homeostasis has been linked to ALS and AD. EC are particularly vulnerable to polyamine imbalance with ATP13A3 loss-of-function mutations being linked to pulmonary hypertension, a disease of EC dysfunction. Recent work shows that ATP13A3 knockout (ATP13A3 KO) in mouse brain EC led to elevated putrescine uptake, likely due to endosomal sequestration. ATP13A3 KO cells also showed reduced VE-cadherin and ZO-1 expression as well as increased leakage to 10kDa Dextran FITC, indicating EC integrity loss. Together, these findings underscore a key role of ATP13A3 in maintaining EC integrity potentially through regulation of polyamine homeostasis.

15. Anirudhya Lahiri

Prevention of peripheral nerve demyelination by immunomodulation in a twitcher mouse model of Krabbe's disease
Anirudhya Lahiri[1], Erica Lavoie[1], Zaenab Dhari[1], Lucille E Papile[1], Jake Lustig[1], Evan Lombardo[1], Ernesto Bongarzone[2], Stephen J Crocker[1]

[1]Department of Neuroscience, University of Connecticut School of Medicine
[2]Department of Anatomy and Cell Biology, University of Illinois College of Medicine, Chicago, Illinois

Krabbe's disease or Globoid cell leukodystrophy (GLD) is a fatal lysosomal storage disorder resulting from a mutation in the galactosylceramidase (GALC) gene. This mutation leads to the toxic accumulation of psychosine, which adversely affects both the central nervous system (CNS) and the peripheral nervous system (PNS). Affected individuals, experience significant demyelination both in the CNS and PNS, which are thought to contributing to premature mortality. Currently, the only FDA-approved treatment for GLD is hematopoietic stem cell transplantation which, while effective has limited availability and long-term benefits. Consequently, there is an urgent need for additional treatment options. We have recently demonstrated that CD8+ T cells play a critical role in the pathophysiology of GLD. Since immunomodulatory therapies targeting T cells have been developed for other demyelinating diseases such as multiple sclerosis (MS), we evaluated the potential utility of repurposing natalizumab, an FDA-approved disease-modifying therapy for treatment of relapsing-remitting MS (RRMS) that inhibits lymphocyte migration into the CNS. We have found that natalizumab effectively extended wellness and prevented PNS demyelination in twitcher mice. Furthermore, flow cytometric analysis confirmed that natalizumab reduced infiltration of effector memory CD8+ T cells in both CNS and PNS when compared with untreated twitcher controls. These results support the consideration

of natalizumab as a viable therapeutic option for treatment of peripheral neuropathology in individuals with GLD.

16. Sanjeev Yadav

Targeting miR-200 Family miRNAs Protects BV2 Microglia Cells Against OGD/Reoxygenation Injury by Restoring the Tgfβ2/Zeb1 Signaling Pathway

Sanjeev Kumar Yadav, PhD[1] Daylin Gamiotea Turro, PhD[1]; and Rajkumar Verma PhD[1]

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Our prior work demonstrated the upregulation of miR-200 family miRNAs specifically miR-141 & miR-200c after stroke in mice models. Moreover, we found a significant upregulation of miR-141 in stroke patient's blood samples and validated the potential of targeting miR-141 to mitigate ischemic stroke damage. In this study, we aimed to validate the upregulation of miR-200c in stroke patients plasma samples and evaluate the potential of inhibiting miR-200c alone or in combination with miR-141 to mitigate stroke damage in oxygen-glucose deprivation (OGD) in microglial BV2 cells. Total RNA (including miRNAs) was isolated from plasma samples of stroke patients and healthy controls and miR-200c expression was assessed by qPCR. In vitro, an oxygen-glucose deprivation (OGD) model in BV2 cells was used to assess the potential of inhibition using antagomiRs of miR-200c alone and in combination with miR-141 on cell viability, cytotoxicity, apoptosis and inflammation via MTT, LDH assays, and qPCR for gene expression. TargetScan web portal was used to obtain the potential targets of miR-200c/141 and explored the molecular mechanism behind this neuroprotection. miR-200c was significantly upregulated in stroke patients compared to healthy individuals, confirming the current study's translational potential. We found a gradual increase in miR-200c expression after 1h, 2h, 3h, and 4h (>5 folds) OGD followed by 24h reperfusion (R). Inhibition of miR-200c or miR-141/200c cluster after 4h OGD/24h R showed a synergistic effect on cell viability and cytotoxicity. Inhibition of the miR-141/200c increased anti-apoptotic gene Bcl2 and reduced the pro-apoptotic (Bax) and pro-inflammatory genes (Il-1β, Il6, and Tnf-α) in BV2 cells following OGD/R. According to TargetScan analysis, Smad2 is a direct target of miR-200c, Tgfb2 is targeted by miR-141, and Zeb1 is commonly targeted by both miR-200c and miR-141-3p; the expression of these genes significantly decreases following OGD/R. The inhibition of miR-141/200c restored the levels of Tgfβ2, Smad2 & Zeb1. Cluster miR-141/200c can act as a biomarker and a prominent therapeutic target for stroke treatment. In vitro, the inhibition of miR-200c alone or together with miR-141-3p protects from OGD-induced injury in microglial BV2 cells by reducing neuroinflammation and apoptosis. Overall, the Tgfβ2/Zeb1 pathway is involved in the cluster miR-141/200c mediated neuroprotection.
Support: This work was supported by NIH (1R21NS114981-01A1) and UConn OVPR (to Rajkumar Verma)

17. Maeva Devoucoux

Alternative splicing of chromatin-modifying factors in breast cancer cells

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Aberrant RNA splicing has emerged as a hallmark of cancer, yet the functional consequences of splicing dysregulation in chromatin regulators remain poorly understood. Here, we investigated the role of alternative splicing in modulating the expression and activity of EZH2, a key histone methyltransferase frequently upregulated in aggressive breast cancers, including triple-negative breast cancer (TNBC). Using the splicing modulator H3B-8800, which targets the SF3b complex of the spliceosome, we perturbed splicing in TNBC cell lines and assessed its impact on EZH2 isoforms. We observed that splicing inhibition preferentially affects

TNBC compared to normal human mammary epithelial cells (HMECs), revealing a cancer-specific vulnerability. In particular, we identified a recurrent intron retention event in EZH2 transcripts that is enriched in TNBC. This event introduces a premature stop codon, potentially leading to reduced EZH2 protein expression. Functional analyses suggest that this mechanism may underlie the heightened sensitivity of TNBC cells to spliceosome inhibition. Our findings highlight a mechanistic link between splicing regulation and chromatin-modifying enzymes, uncovering a potential therapeutic strategy to selectively downregulate EZH2 in cancer. Importantly, targeting splicing to induce intron retention in EZH2 could represent an alternative to current EZH2 inhibitors, which either block its catalytic SET domain—risking off-target effects on EZH1—or disrupt its role in the PRC2 complex without addressing noncanonical functions. By contrast, splicing-based strategies may offer greater specificity and broader impact on EZH2 biology. Together, this work provides new insight into how splicing modulation can reshape the chromatin landscape in breast cancer and establishes the foundation for developing antisense oligonucleotide approaches to therapeutically exploit splicing-mediated vulnerabilities in EZH2 and other chromatin regulators.

18. Luke Trinity

CMVerify: Accurate prediction of CMV serostatus from human PBMCs single cell RNA-seq

Luke Trinity[1], Titas Grabauskas[1,2], Djamel Nehar-Belaid[1], Asa Thibodeau[1], Giray Eryilmaz[1], Jacques Banchereau[1,3], George A Kuchel[4,5], Duygu Ucar[1,5]

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Cytomegalovirus (CMV) is a persistent herpesvirus that establishes lifelong latency in myeloid progenitor cells. Despite an estimated global seropositivity of over 80%, CMV confounds immune aging research due to its extensive remodeling of immune cell populations. To disentangle the effects of CMV on the immune system across the human life span, we annotated over 15 million peripheral blood mononuclear cells (PBMCs) from three independent cohorts (ages 11-88). We identify a distinct signature of CMV-associated immune alterations based on changes in cell type compositions which contrasts with age associated immune alterations. To control for CMV-driven immune alterations in studies where donor CMV status is unknown, we developed CMVerify, a model that accurately predicts CMV serostatus using only PBMC proportions as input. CMVerify achieved >90% accuracy in predicting CMV serostatus for unseen test samples, demonstrating robust and stable performance across age groups, including longitudinal validation. Our model also successfully identified a seroconversion event, highlighting its precise efficacy on an individual, per sample basis. CMVerify is a novel and essential tool for predicting CMV serostatus, enabling researchers to account for the confounding effects of CMV on immune aging research.

19. Xuan Ye

Comprehensive characterization of snoRNAs and their 2'-O-Methylation signatures in *Drosophila melanogaster*

Xuan Ye[1], Sara Olson[1], Yaling Liu[1], Lijun Zhan[1], Gordon Carmichael[1], Brenton Graveley[1]

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Small nucleolar RNAs (snoRNAs) are a class of non-coding RNAs ranging from 49 to 511 nt in length that play critical roles in guiding 2'-O-methylation (Nm) and pseudouridylation modifications of RNAs. In *Drosophila melanogaster*, snoRNA expression is known to undergo dynamic changes during development,

yet a comprehensive atlas of snoRNA expression and activity in cellular contexts has been lacking. In this study, we profiled snoRNA expression in *Drosophila* S2 cell lines using small RNA sequencing, employing the Group II intron reverse transcriptase ultraMarathonRT to enhance detection fidelity. Our analysis identified 239 snoRNAs with robust expression, representing 87% of all annotated *Drosophila* snoRNAs, and providing a detailed expression landscape in this model system. Given that C/D box snoRNAs guide site-specific 2'-O-methylation of RNA, we further characterized the Nm landscape using RibOxi-Seq, a high-throughput approach capable of detecting Nm modifications with single-nucleotide resolution. RibOxi-Seq revealed 17 Nm sites in the 18S rRNA with a 94% concordance to previously reported RiboMeth-Seq data. In the 28S rRNA, 37 Nm sites were identified, corresponding to an 88% overlap with established references. Additionally, we detected both a known Nm site (Gm74) and a novel site (Um66) in 5.8S rRNA, further validating the sensitivity and specificity of the approach. Additionally, the method revealed Nm modifications within internal regions of mRNAs. In total, we detected Nm modifications in 3,691 unique mRNAs, underscoring the widespread presence of this epitranscriptomic modification in coding transcripts. Collectively, our study presents a comprehensive atlas of snoRNA expression and their associated 2'-O-methylation activity in *Drosophila* S2 cells, offering valuable insights into the epitranscriptomic landscape orchestrated by snoRNAs.

20. Su Xu

Harmonizing spatial transcriptomic data across multiple brain slices via two-stage pseudo-image registration

Su Xu[1], Dongyuan Song[1]

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Aligning spatial transcriptomics (ST) data across multiple tissue sections poses challenges due to anatomical variability and technical noise. We present a two-stage framework to harmonize ST data from mouse brain slices by combining biological structure discovery with image registration. In the first stage, we perform joint niche identification using shared embedding and clustering to define conserved spatial domains across samples. In the second stage, we convert the labeled spatial coordinates into pseudo-images with distinguishable colors, which are then aligned using affine and diffeomorphic transformations. While inspired by image registration, our approach operates on biologically derived pseudo-images rather than histological data or cell density plot. This framework improves cross-sample alignment, enabling consistent spatial domain detection and facilitating downstream analyses such as region or location-specific differential expression (DE) analysis. Our method is scalable, interpretable, and broadly applicable to multi-sample ST integration tasks.

21. Wenqiang Du

Aberrant matrix signals at scar cause Piezo1 driven NF-κB mediated inflammation promoting accreta-like deep placental invasion

Wenqiang Du[1,2], Ashkan Novin[1,2], Junaid Afzal[3], Yamin Liu[2], Yasir Suhail[1,2], Shaofei Liu[1,2], Nicole R. Gavin[4], Jennifer Jorgensen[4], Christopher M Morosky[4], Reinaldo Figueroa[5], Tannin Schmidt[1], Melinda Sanders[4,6], Molly Brewer[4], Kshitiz[1,2]

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Scar tissue formation is a hallmark of wound repair in adults and can chronically affect tissue architecture and function. To understand the general phenomena, we sought to explore scar-driven imbalance in tissue homeostasis caused by a common, and standardized surgical procedure, the uterine scar due to cesarean surgery. Deep uterine scar is associated with a rapidly increasing condition in pregnant women, placenta accreta spectrum (PAS), characterized by aggressive trophoblast invasion into the uterus, frequently necessitating hysterectomy at parturition. We created a model of uterine scar, recapitulating PAS-like invasive phenotype, showing that scar matrix activates mechanosensitive ion channel, Piezo1, through glycolysis-fueled cellular contraction. Piezo1 activation increases intracellular calcium activity and Protein kinase C activation, leading to NF-κB nuclear translocation, and MafG stabilization. This inflammatory transformation of decidua leads to production of IL-8 and G-CSF, chemotactically recruiting invading trophoblasts towards scar, initiating PAS. Our study demonstrates aberrant mechanics of scar disturbs stroma-epithelia homeostasis in placentation, with implications in cancer dissemination.

22. Caroline Haney

Spatial insights into endometriosis: mapping fibroblast and neuroimmune niches involved in pain.
Caroline M. Haney[1], Elaheh Alizadeh[1], Meryl Sullivan[1,2], Joshua Lee[1,2], Jasmina Kuljancic[1], William F. Flynn[1], Paul Robson[1,2], Brian S. White[1], Danielle E. Luciano[2], Elise T. Courtois[1,2]

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Endometriosis is a common, chronic inflammatory condition where tissue similar to the uterine lining grows outside the uterus, termed lesions, often causing persistent pain and reduced quality of life. Despite affecting at least one in ten female-born individuals, the biological mechanisms behind its symptoms and progression remain poorly understood. In this study, we used high-resolution spatial transcriptomics to map the cellular landscape of human ovarian and peritoneal endometriosis lesions, two of the most common lesion types. Across lesion types, we found consistent patterns, including clusters of immune cells, fibroblast-rich zones surrounding epithelial glands, and distinct distributions of nerve and macrophage cell types. We identified specific sensory neuron subtypes – nociceptor, mechanoreceptor, proprioceptor and sympathetic neurons - and mapped their spatial relationships with nearby immune cells - in particular macrophages. We observed sensory nociceptor neurons in close proximity to epithelial glands and MME+ fibroblasts. To further explore how these cells interact, we developed a 3D cellular co-culture model combining IPSC-derived peripheral sensory brain organoids with patient-derived endometriosis epithelial and fibroblast cells. We evaluated in this in vitro model the neurogenic impact of epithelial and fibroblast cells by bulk RNA sequencing. We found increased sensory neuron and decreased sympathetic neuron states in a similar manner as observed in vivo. This allowed us to validate key cellular interactions that may contribute to pain. Our strategy enables the identification of common features across various lesion locations and compositions. By revealing conserved cellular features and interactions linked to symptoms, our findings offer new insights into endometriosis biology and highlight potential targets for future therapies.

23. Corie Owen

Luteinizing hormone-induced interfollicular communication in the mouse ovary
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In mammalian ovaries, oocytes are maintained in meiotic arrest within individual units known as follicles. Within each follicle, the oocyte is surrounded by multiple layers of somatic cells known as granulosa cells, all

encased in a basal lamina. Outside of the basal lamina are theca cells and interstitial cells, which support the developing follicles. Each reproductive cycle, a subset of follicles will grow until one, or more, depending on the species, reaches the preovulatory stage. At the preovulatory stage, the follicles will respond to luteinizing hormone (LH), which stimulates meiotic resumption and ovulation of the oocyte in preparation for fertilization. Receptors for luteinizing hormone are expressed in the outer mural granulosa cells of fully grown follicles, and in some theca and interstitial cells. While LH receptors in the mural granulosa cells of an individual follicle are sufficient to mediate meiotic resumption in response to LH, the presence of LH receptors throughout the ovary raises the question of whether LH receptors outside of an individual follicle can also contribute to ovulatory responses in that follicle. To investigate this question, we asked whether isolated follicles lacking LH receptors could respond to LH if co-cultured with wildtype follicles. To do this, we generated a mouse line in which the LH receptor was deleted. As expected, follicles from *Lhr*-knockout mice failed to respond to LH. However, when placed on an organotypic membrane in contact with wildtype follicles, *Lhr*-knockout follicles resumed meiosis in response to LH. These findings indicate that the ovary responds holistically to the LH surge, with individual follicles responding not only to LH directly, but also to paracrine signals generated by other follicles to ensure successful meiotic resumption.

24. Everton Bettin

Use of multivalent scaffolds displaying *Treponema pallidum* outer membrane protein extracellular loops as candidate syphilis vaccinogens.

Everton Bettin[1], Renee Pontbriant[1], Morgan LeDoyt[1], Justin D. Radolf[1,2], Kelly L. Hawley[1,2] and Melissa J. Caimano[1]

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The rising incidence of syphilis underscores the urgent need for a vaccine to prevent transmission of *Treponema pallidum* subsp. *pallidum* (*TPA*). An effective vaccine should elicit functional antibodies (*i.e.*, opsonic and/or neutralizing) against extracellular loops (ECLs) of the spirochete's limited repertoire of outer membrane proteins (OMPs). Using a *Pyrococcus furiosus* thioredoxin (*Pf*Trx) scaffold presenting individual ECLs, we previously identified *TPA* regions that are highly immunogenic during human infection and capable of inducing functional antibodies upon rabbit immunization. However, a broad and long-lasting protection will likely require a multivalent vaccine cocktail containing multiple *TPA* ECLs in their native conformation. To this end, we engineered a truncated eight-stranded beta-barrel (8Sβb) OmpA (OmpAtr) from *Escherichia coli* and the C-lobe of the transferrin binding protein B (TbpB) from *Neisseria meningitidis* as scaffolds to present up to four *TPA* ECLs in a native-like conformation. Specifically, ECLs 2 and 4 from the FadL-like transporters TP0856 and TP0858 were grafted onto both scaffolds, while all four ECLs from the *TPA* 8Sβb proteins TP0698 and TP0733 were grafted onto OmpAtr. Recombinant multi-ECL constructs were expressed in *E. coli* and successfully refolded into their native conformations. Rabbits immunized with the purified proteins generated robust ECL-specific antibody titers against multiple ECLs, as measured by Western blot and ELISA. Importantly, the presence of multiple ECLs from the same OMP did not diminish the production of antibodies against the individual components, with titers comparable to or greater than those elicited by single-ECL PfTrx constructs. These findings support the use of multivalent scaffolds displaying *TPA* ECLs as promising vaccine candidates for inducing broad and potent immune responses. Ongoing studies are evaluating the opsonic and neutralizing activities of antibodies elicited by multi-ECL scaffolds in comparison with results previously achieved using single-ECL constructs.

25. Ali Zelan

Social validity assessment in early childhood intervention
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Social validity is a construct representing the social and practical value of products, including programs, services, and interventions. The term “social validity" was coined in the field of applied behavior analysis and is widely accepted across other education and health sciences. Social validity is often associated with various key components in research and practice, affecting both internal and external validity. Assessing and reporting social validity is recognized as an important and necessary process. However, research, including numerous systematic literature reviews, shows that addressing social validity is often neglected in intervention studies published across various fields. Using surveys and interviews, we investigated how special education and early childhood intervention researchers perceive and address social validity, as well as the factors affecting how it is addressed. Findings show that while most researchers support the recommendations provided in the literature, they do not apply them in their research. Findings also indicate that there are systematic barriers and incentive structures that lead researchers to use traditional methods of assessing social validity, even though they acknowledge the superiority of more authentic approaches.

26. Emilie Butler

Managing Anxiety in Pediatric Primary Care (MAPP): Preliminary outcomes of a pilot RCT
Emilie J. Butler[1]*, Golda S. Ginsburg*[1]

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Pediatric anxiety disorders are the most common psychiatric illnesses and are linked to impairment in social, academic, familial, and personal functioning. Despite this, less than half of anxious youth receive mental health services. One approach to addressing this gap is to shift anxiety interventions to be delivered by non-mental health specialists in settings youth frequent. This poster and brief presentation describe preliminary outcomes of an ongoing NIMH-funded RCT evaluating the *Managing Anxiety in Pediatric Primary Care* (MAPP) program, a brief primary care provider (PCP) delivered intervention compared to Enhanced Usual Care (online anxiety reduction resources) for youth (ages 6-17) with impairing anxiety. Primary care settings are ideal for addressing pediatric anxiety due to the high prevalence rates (approximately 10-20%), the high proportion of physical complaints (e.g., stomach aches) reported by youth with anxiety, and the higher likelihood of youth with, compared to without, medical conditions have elevated anxiety. Additionally, PCPs are often the first and only provider that youth with anxiety visit regularly. MAPP involves psychoeducation, exposure, and parenting strategies, and is delivered over one to four 20- to 30-minute sessions. Thus far, 37 PCPs (M_{age}=44, 86% female; 71% White) have been enrolled. Preliminary outcomes assessed PCP adherence and youth pre-post anxiety outcomes. Results demonstrated that PCPs delivered MAPP with “fair” to “good” adherence quality based on audio taped coded sessions. Pre-post youth outcome data with 41 youth (ages 6-17; 73% female; 80% White) suggest that both MAPP and EUC result in significant reductions in youth anxiety based on parent and independent-evaluator report. Enhancing the capacity of PCPs to identify and intervene with anxious youth appears promising based on these preliminary findings. The absence of group differences raises questions about the mechanisms of youth improvement, which will be examined in future studies.

27. Bridget Hayes

Functional Impairment in Daily Living during Long-Term Remission from Substance Use Disorders

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Aim: Substance use disorders (SUD) frequently cause functional impairment in daily living (FIDL), e.g., problems with meeting expectations at work, in social interactions, and with self-care. It has often been speculated that FIDL could persist even during periods of remission from SUD, and that persistent FIDL may constitute a risk factor for return to harmful substance use. The aim of this research was to test the hypothesis that remitted people experience more problems with daily living than people with no history of SUD using a validated measure of functional disability (The World Health Organization Disability Assessment Schedule [WHODAS]). Problems associated with acute mental illness were also examined as an alternative explanation for functional impairment.
Method: A nationally-representative sample of 9,925 remitted people – defined as no longer meeting criteria for SUD during the prior 12 months – and 92,228 people with no lifetime SUD was obtained from the National Survey on Drug Use and Health (NSDUH, years 2018-2020). Hierarchical generalized linear models estimated the association between WHODAS score and remission status, current mental illness, substance use, and sociodemographic factors.
Results: Serious mental illness was twice as prevalent in the remitted sample (18.2% v. 9.4%). Remitted people reported more FIDL than those with no prior SUD (unadjusted mean WHODAS = 5.54 v. 3.12). However, controlling for mental illness reduced the difference in FIDL associated with remitted SUD to approximately 1.14 points on the 24-point WHODAS scale. By comparison, serious mental illness was associated with an approximately 8-point higher score on WHODAS.
Conclusion: Sustained remission from SUD is associated with a measurable but small elevation in problems with daily living. Low functioning during remission may often be attributable to current mental illness rather than residual effects of SUD per se.

28. Yurui Zheng

4-hydroxyphenylacetic acid, a microbial metabolite, reduces alcohol-induced inflammation via dual modulation of NF-κB and Interferon pathways

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Chronic alcohol consumption is a major factor in triggering inflammatory responses, particularly in the liver, intestine, and immune system. One key inducer of inflammation is gut-derived lipopolysaccharide (LPS), which is increased during alcohol consumption. In return, LPS activates pro-inflammatory pathways such nuclear factor kappa B (NF-κB) in immune cells like monocytes and macrophages. THP1-Dual cells are a monocyte cell line that have been engineered to contain dual reporter systems, allowing the study of both NF-κB, via secreted embryonic alkaline phosphatase (SEAP), and interferon regulatory factor (IRF) pathways, via luciferase (Lucia). Using these cells, we found that alcohol can modify gene expression networks resulting in increased NF-κB signaling, and reduced IRF signaling. To identify novel drugs that modulate these pathways, we challenged THP1-Dual cells with +/- LPS (100pg/ml) to simulate chronic inflammation observed in patients. After 24 hours, cells were then treated with a single compound from a library of microbial metabolites. After another 24-hours, we collected supernatant to measure SEAP and Lucia. We found that 4-Hydroxyphenylacetic acid (4-HPAA), a microbial metabolite with a phenolic structure, led to a downregulation of NF-κB and an upregulation of IFN pathway activity, suggesting a dual modulatory role. To further elucidate

the mechanism of action, quantitative PCR (qPCR) analysis was performed on inflammation-related genes downstream of both NF-KB and interferon. Compared to the control group, 4-HPAA treatment resulted in significant inhibition of pro-inflammatory genes such as IL-1β, TNF-α, supporting its anti-inflammatory efficacy. These findings provide insight into the potential application of 4-HPAA as a therapeutic agent targeting on alcohol-induced inflammation.

29. Naushad Khan

Enhancing HIV Immunotherapy through Advanced NK Cell Engineering

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Human Immunodeficiency Virus (HIV) is an incurable viral disease that remains a major global health challenge. According to WHO, HIV has caused over 44 million deaths globally to date and about 1.3 million new HIV infections and 630,000 HIV-related deaths in 2024. HIV progressively impairs the immune system by depleting CD4+ T helper cells, leading to increased susceptibility to opportunistic infections and acquired immunodeficiency syndrome (AIDS)-related malignancies. Preventive strategies include pre-exposure prophylaxis aimed to reduce risk of infection in high-risk populations, while antiretroviral therapy to reduce viral titers and preserve immune function. Natural killer (NK) cells are innate lymphocytes now recognized as critical regulators of antiviral immunity with adaptive immune properties. They mediate antiviral immunity through the production of cytokines, chemokines, and cytolytic molecules. NK cells are diverse in phenotype and function and are increasingly utilized as immunotherapy products. The goal of this project is to identify the NK cell subset most responsive to HIV for therapeutic development. To this end, we vaccinated hematopoietic stem cell (HSC) immune system-humanized IL-15-transgenic NOD/SCID/IL-2Rg-deficient (NSG-Tg(Hu-IL15) mice with HIV envelope protein (HIV-Env), or with HIV unrelated antigens (controls) and identified cell surface receptors uniquely expressed by HIV-Env primed NK cells by single cell RNA sequencing and flow cytometry protein-expression verification and determined the relevance of each molecule in NK cell subsets expressing or devoid of these proteins and tested their ability to suppress HIV replication in vitro and in vivo. Here, we demonstrate that weekly infusions of NK cell (subsets) suppress HIV viral titers in vitro and in humanized mice. Liver-resident NK cells also exhibited antigen-specific memory by recognizing HIV Env antigen post-vaccination, highlighting their potential for long term HIV control and application in future immunotherapy.

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