19th ANNUAL POSTDOC SYMPOSIUM

October 14, 2025

Student Life Center

VANDERBILT

Vanderbilt Postdoctoral Association

Sponsored by Office of Postdoctoral Affairs

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FOREWORD

The Vanderbilt Postdoctoral Association (VPA) was founded in 1998 as a mechanism to support the professional, personal, and scholarly success of postdocs from **Vanderbilt University** and **Vanderbilt University Medical Center.** Since then, the VPA has organized 18 annual symposia, highlighting the works of hundreds of previous postdoctoral scholars. Over this past year, we have had a dedicated group of postdocs from both VU and VUMC working together to make our **19th Annual VPA Symposium** an interactive experience for postdocs who call Vanderbilt home.

Disseminating science through conferences is a powerful way to share diverse perspectives and tackle some of humanity's most challenging problems. This symposium brings together research from various departments at Vanderbilt University - including Medicine, Earth and Environmental Sciences, Electrical and Computer Engineering, and Physics and Astronomy, fostering an environment where our postdoc community can explore different disciplines and generate innovative ideas. Such cross-disciplinary awareness is vital for addressing pressing issues in society and it is through our collective efforts that we can achieve the extraordinary.

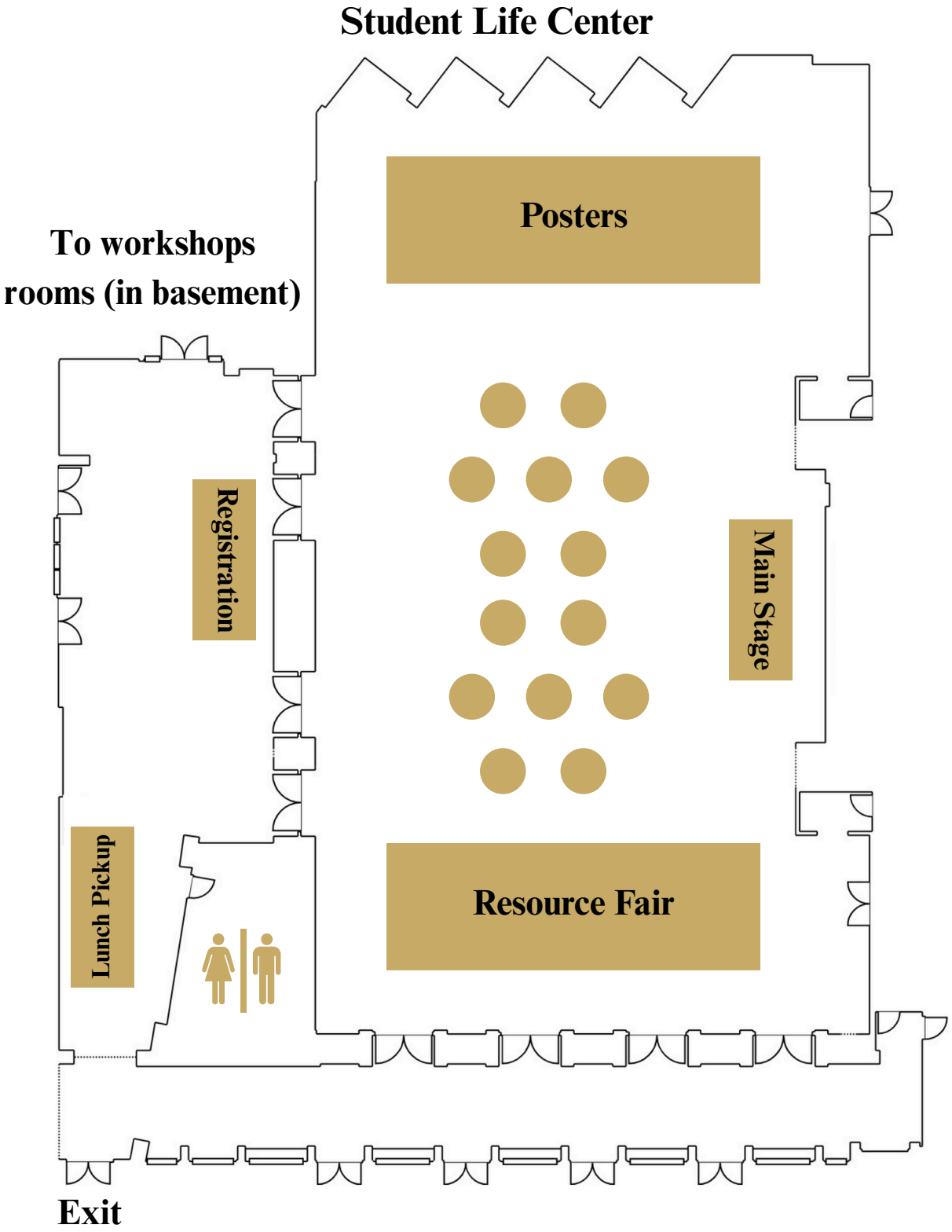
We are immensely grateful to **Dr. Matthew Johnson-Roberson**, the inauguaral Dean of Vanderbilt University's College of Connected Computing, for accepting our invitation as keynote speaker despite his busy schedule. We also extend our appreciation to all the Vanderbilt faculty and staff who agreed to contribute their time and expertise through workshops and lectures for this event.

This symposium would not be possible without the collective efforts of the organizing committee, the enthusiastic community of postdocs eager to share their work through poster presentations and lightning talks, and all the attendees. We hope to convey that each one of you is essential and plays a pivotal role in shaping the future. **On behalf of the Vanderbilt Postdoctoral Association and the symposium planning committee, we hope this day provides ample opportunities for scientific discovery, collaboration, and networking.**

SCHEDULE OF EVENTS

9:15AM to 9:30AM	**Welcome Remarks** **Dr. C. André Christie-Mizell, PhD** Vice Provost for Graduate Education, Dean of the Graduate School, Director of the Office of Postdoctoral Affairs	
9:30AM to 10:30AM	**Reimagining Academic Inquiry: Emerging AI for the Research Toolkit** **Dr. Charreau Bell, PhD** Professor, Computer Science, Vanderbilt University and Senior Data Scientist, Data Science Institute, Vanderbilt University	
10:30AM to 11:30AM	**Poster Session #1**	**Resource Fair**
11:30AM to 1:00PM	**Lunch Keynote Address: Artificial Intelligence : History, Future, and the Role of Vanderbilt's College of Connected Computing in shaping it** **Dr. Matthew Johnson-Roberson, PhD** Dean of the College of Connected Computing, University Distinguished Professor of Computer Science, University Distinguished Professor of Electrical and Computer Engineering, Vanderbilt University	
1:00PM to 1:15PM	**Break**	
1:15PM to 2:00PM	**Poster Session #2**	**Resource Fair**
2:00PM to 3:00PM	**Workshop 1: The Policy Pipeline : a conversation about past insights, present challenges, and future advocates** **Dr. Heather Bloemhard, PhD**	**Workshop 2: Lessons from the Science of Motivation: A Simple, Leverageable Framework for Leaders** **Dr. Christine Quinn Trank, PhD** **Dr. Susan Douglas, PhD**
3:00PM to 4:30PM	**Lightning Talks**	
4:30PM to 5:00PM	**Closing Remarks, Award Ceremony, & Social Gathering**	

SYMPOSIUM VENUE OVERVIEW



WELCOMING REMARKS

Dr. C. André Christie-Mizell, PhD
Vice Provost for Graduate Education
Dean of the Graduate School
Director of the Office of Postdoctoral Affairs Centennial
Professor of Sociology
Vanderbilt University

Dr. C. André Christie-Mizell serves as the Vice Provost for Graduate Education, Dean of the Graduate School, and Director of the Office of Postdoctoral Affairs at Vanderbilt University. Since joining Vanderbilt's Department of Sociology in 2010, he has focused on enhancing the support and resources available to postdoctoral scholars. His leadership has led to the implementation of innovative funding models and pipeline programs aimed at diversifying the academic workforce and ensuring robust career pathways for graduate and postdoctoral students. Notably, he established the Vanderbilt-Fisk Joint Postdoctoral Fellowship Program, fostering collaboration between institutions and preparing scholars for academic careers. Christie-Mizell's unwavering commitment to equity, diversity, and inclusion is central to his mission of improving postdoctoral experiences and outcomes, ultimately shaping the next generation of academic leaders.

The postdoc community at Vanderbilt is truly fortunate to benefit from Dr. Christie-Mizell's dedicated leadership, unwavering support, and commitment to enhancing our academic and professional growth.

REIMAGINING ACADEMIC INQUIRY: EMERGING AI FOR THE RESEARCH TOOLKIT

Dr. Charreau Bell, PhD
Professor, Computer Science
Senior Data Scientist, Data Science Institute
Vanderbilt University

Bio:

Charreau Bell, PhD is the Director of the Undergraduate Data Science Program, an Assistant Professor of the Practice of Computer Science, and a Senior Data Scientist at the Data Science Institute (DSI) at Vanderbilt University. In her current role, she leads several data science projects across a spectrum of disciplines using generative artificial intelligence (AI), transformers, deep learning, and data science. At the DSI, Dr. Bell has engaged with industry partners, faculty, staff, postdoctoral researchers, and students in AI and data science projects in areas including law, history, archaeology, sustainability, health care, social good, and education. She is a consultant for researchers and industry organizations to help form, plan, evaluate, and reach data-driven academic or business objectives.

Prior to joining the DSI, she earned her Doctorate, Master's, and Bachelor's degrees in engineering from Vanderbilt University. Her Ph.D. focused on creating new algorithms for understanding the resting state behavior of the brain using functional brain imaging technology. She also taught computer science courses at Tennessee State University as an adjunct professor, and interned with NASA implementing machine learning and other optimization algorithms for robotic systems and instrument sensorization.

REIMAGINING ACADEMIC INQUIRY: EMERGING AI FOR THE RESEARCH TOOLKIT

Dr. Charreau Bell, PhD
Professor, Computer Science
Senior Data Scientist, Data Science Institute
Vanderbilt University

Abstract:

Yesterday's science fiction is today's research toolkit. Artificial intelligence (AI) can help researchers move past technical roadblocks, frame questions in new ways, and bring clarity and creativity to every stage of scholarship. But what tools are even out there? And how do they relate to core research activities? In this session, we will explore the broad landscape of AI resources available now: large language model (LLM) platforms, tools that support common research tasks, and emerging technologies that add new dimensions to traditional research approaches. We'll highlight tools that stretch from the familiar to the unconventional, including platforms for deep research, structured prompt experimentation, and even building your own custom systems for presenting and sharing research. You'll walk away with a clearer view of the AI landscape - what tools and resources are out there, what they can do – and inspiration to reimagine the workflows that shape your academic research.

KEYNOTE

Dr. Matthew Johnson-Roberson, PhD
Dean of the College of Connected Computing
University Distinguished Professor
of Computer Science
University Distinguished Professor
of Electrical and Computer Engineering
Vanderbilt University

Dr. Matthew Johnson-Roberson, PhD is the inaugural Dean of Vanderbilt University's College of Connected Computing and a University Distinguished Professor with joint appointments in the College of Connected Computing and the School of Engineering. A visionary scholar and accomplished academic leader, Dr. Johnson-Roberson brings deep expertise in robotics, computer vision, machine learning, and autonomous systems. Prior to joining Vanderbilt, Dr. Johnson-Roberson was a Professor in the Naval Architecture and Marine Engineering department with a joint appointment in Computer Science and Engineering at University of Michigan College of Engineering, where he was also the founding director of the Ford Center for Autonomous Vehicles. He then served as director of Carnegie Mellon University's world-renowned Robotics Institute. He has led large-scale research initiatives, including a $45 million grant to build CMU's Robotics Innovation Center, and has developed partnerships with industry leaders such as Google, Amazon, and Ford.

Dr. Johnson-Roberson's leadership is guided by a commitment to interdisciplinary collaboration and the principle of "Computing for All" aiming to advance cutting-edge discovery and inclusive education across fields like AI, digital humanities, data analytics, and beyond.

WORKSHOP 1

Dr. Heather Bloemhard, PhD
Director of Federal Relations
Vanderbilt University's Office of Federal Relations

The Policy Pipeline, a conversation about past insights, present challenges, and future advocates

Are you curious what a career in science policy might look like? What to know how to be civically engaged - but not necessarily change your career path? Or have questions about specific policies? Bloemhard will share her career trajectory to science policy, provide an overview of the current policy landscape, and discuss how you can be engaged in policy conversations. Come with questions!

WORKSHOP 2

Dr. Christine Quinn Trank, PhD
Associate Professor, Practice, Department of Leadership, Policy, and Organizations
Vanderbilt Peabody College of Education and Human Development

Dr. Susan Douglas, PhD
Professor, Practice, Department of Leadership, Policy, and Organizations
Vanderbilt Peabody College of Education and Human Development

Lessons from the Science of Motivation: A Simple, Leverageable Framework for Leaders

In this one-hour workshop, we introduce you to a simple, evidence-based approach to understanding what motivates people – and how to use it to achieve better results and create an energized workplace. Participants will explore core drivers of motivation, reflect on their own experiences, and practice applying the framework to common mentoring and workplace challenges. The session is highly interactive, designed to leave participants with practical tools they can immediately use to inspire and support those they lead and with whom the collaborate.

RESOURCE FAIR

Morning (M) Session: 10:30 - 11:30 AM
Afternoon (A) Session: 1:15 - 2:00 PM

Organization	Info	Session
Field Specific		
BioVU	https://victr.vumc.org/what-is-biovu/	A
Cell Imaging Shared Resource (CISR)	https://medschool.vanderbilt.edu/cisr/	M, A
ResearchMatch	https://www.researchmatch.org	M, A
VANTAGE (Next Generation Sequencing Core)	https://www.vumc.org/vantage/next-gen-sequencing	M, A
Vanderbilt Center for Technology Transfer and Commercialization	https://cttc.co	M
Professional Development		
BRET Office	https://medschool.vanderbilt.edu/bret/	M, A
Edge for Scholars	https://edgeforscholars.vumc.org	M
English Language Center	https://www.vanderbilt.edu/elc/	M, A
Graduate and Postdoctoral Career Success	https://www.vanderbilt.edu/career/graduate-students-scholars/	M, A
Graduate and Postdoc Academic Success (GPAS)	https://gradschool.vanderbilt.edu/student-resources/professional-development/gpas/	M, A
Vanderbilt Libraries	https://www.library.vanderbilt.edu	A
Writing Studio and Tutoring Services	https://www.vanderbilt.edu/writing/	M, A

RESOURCE FAIR

Morning (M) Session: 10:30 - 11:30 AM
Afternoon (A) Session: 1:15 - 2:00 PM

Organization	Info	Session
Health and Welllness		
Health, Wellbeing & Belonging	https://www.vanderbilt.edu/healthwellness/	M
Housing and Relocation Coordinator	https://www.vanderbilt.edu/healthwellness/people-and-areas/housing-and-relocation-coordinator/	A
Margaret Cuninggim Women's Center	https://www.vanderbilt.edu/womenscenter/	M
Project Safe Center	https://www.vanderbilt.edu/projectsafe/	M, A
VUMC Health & Wellness	https://www.vumc.org/hw/vumc-health-wellness	A
International Scholar Resources		
Employee Immigration Services	https://hr.vanderbilt.edu/employee-immigration-services/	M, A
International Student & Scholar Services	https://www.vanderbilt.edu/isss/	A
Vanderbilt Safety Departments		
VU Public Safety Office of Emergency Management	https://publicsafety.vanderbilt.edu	M, A
Financial Services		
Vanderbilt Credit Union	https://vanderbiltcu.org	M, A

RESOURCE FAIR MORNING MAP

MAIN STAGE

9	Health, Wellbeing & Belonging
10	Margaret Cuninggim Women's Center
11	Employee Immigration Services
12	Vanderbilt Center for Technology Transfer and Commercialization (CTTC)
13	ResearchMatch
14	Cell Imaging Shared Resource (CISR)
15	VANTAGE (Next Generation Sequencing Core)
16	Vanderbilt Credit Union
1	Graduate and Postdoctoral Career Success
2	Graduate and Postdoc Academic Success (GPAS)
3	Edge for Scholars
4	BRET Office
5	English Language Center
6	Writing Studio and Tutoring Services
7	VU Public Safety Office of Emergency Management
8	Project Safe Center

EXIT

RESOURCE FAIR AFTERNOON MAP

MAIN STAGE

9	VUMC Health & Wellness	1	Graduate and Postdoctoral Career Success
10	Housing and Relocation Coordinator	2	Graduate and Postdoc Academic Success (GPAS)
11	Employee Immigration Services	3	Vanderbilt Libraries
12	International Student & Scholar Services	4	BRET Office
13	ResearchMatch	5	English Language Center
14	Cell Imaging Shared Resource (CISR)	6	Writing Studio and Tutoring Services
15	VANTAGE (Next Generation Sequencing Core)	7	VU Public Safety Office of Emergency Management
16	Vanderbilt Credit Union	8	Project Safe Center
17	BioVU		

EXIT

LIGHTNING TALKS

Speaker	Talk Title
Al Borhan Bayazid	Rac1 controls cilia-dependent mechanosensing to enhance kidney tubular differentiation after birth
Milene Fontes	The Role of GPNMB in Infection-Mediated Endothelial Dysfunction
Deepika Jayaprakash	Mechanistic basis of biphasic DNA replication fork progression in unperturbed S phase
Anyah Prasad	Social Network Profiles and Self-Perceptions of Aging among LGBTQ+ Older Adults
Javier Ramirez-Ricardo	The cell adhesion protein ALCAM controls the cargo composition of EVs
HyunBin You	Need for a Roadmap: ICU Survivor Insights on Post-Discharge Recovery
Kirill Zavalin	4-Phenylbutyrate Treatment for Pathologic Changes in GABAergic Neurotransmission in Slc6a1+/S295L and Gabrg2+/Q390X Mouse Models of Genetic Epilepsy

POSTER SESSION SCHEDULE

Morning (M) Session: 10:30 - 11:30 AM (Odd Numbers)
Afternoon (A) Session: 1:15 - 2:00 PM (Even Numbers)

Poster Number	Name	Title
1	**Sunday Olatunji**	Mechanisms Underlying Allopregnanolone Modulation of Inhibitory and Excitatory Neurotransmission
2	**Matias Martinez**	Children's peer relationships and caregiver's mental health: Longitudinal associations and persistence of negative relationships
3	**Angusha Dutta**	Dissecting the structural intricacies and molecular choreography of Mla system-mediated phospholipid transport in Gram-negative bacteria
4	**Elizabeth Keeling**	Spinal level-dependent characterization of functional connectivity in the lumbosacral spinal cord in relapsing-remitting multiple sclerosis
5	**William Simke**	Biosynthesis of peptide natural products
6	**Jahnu Saikia**	Optimized albumin-piggybacking strategy enhances ultra-short peptide delivery and bioavailability in a PTOA mouse model
7	**Naomi Rapier-Sharman**	Immune Imbalance Transcriptomics
8	**Withdrawn**	
9	**Nongyao Nonpanya**	Defining cellular compartments of human pediatric pancreatic islets by spatial proteomics
10	**Dan Hao**	Monophosphoryl lipid A boosts macrophages antimicrobial immunity through metabolically regulating source-specific ROS generation
11	**Silvana Bellotto**	The Effect of Ansa Cervicalis Stimulation on Velopharyngeal Cross-sectional Area in Patients with Obstructive Sleep Apnea
12	**Withdrawn**	
13	**Zoe Petros**	Characterization and validation of PROTACs that recruit KLHL12
14	**Mayumi Saiki**	Comparison of Adherence to Self-Care Behaviors between Unemployed and Employed Black Informal Caregivers
15	**Harsh Shah**	Ingestive Behaviors and Energy Homeostasis During and After GLP-1R Agonist Treatment in Mice

POSTER SESSION SCHEDULE

Morning (M) Session: 10:30 - 11:30 AM (Odd Numbers)
Afternoon (A) Session: 1:15 - 2:00 PM (Even Numbers)

Poster Number	Name	Title
16	Anjali Yelikar	Multimessenger and Multiband prospects for binary neutron stars from the Moon
17	Alexander Kwiatkowski	RIG-I Activating Nanoparticles for Glioblastoma Immunotherapy
18	Madhushi Ratnayake	High-Throughput Selection of Conformation-Specific Nanobodies Targeting EGFR
19	Anastasia Varanko	Targeted STING Activation in Regulatory T Cells via Bispecific Nanobody Conjugates to Enhance Anti-Tumor Immunity
20	Charmaine Rock	Limited contribution of sex and sex hormones to regulation of the mouse ductus arteriosus (DA) and human PDA
21	Sunday Olatunji	Synaptic Mechanisms Underlying Allopregnanolone Modulation of Inhibitory and Excitatory Transmission
22	Jessica Rampy	Overnutrition directly disrupts thyroid hormone biosynthesis, despite remarkable thyroidal adaptations
23	Tri Do	Mechanistic Investigation of Intracellular Calcium Release Channel RyR2 Inhibitor Cyclic-Oligomeric Depsipeptides as Therapeutic Treatment for Arrhythmogenic Heart Diseases
24	Rebekah Stanton	An investigation into how microbial communities are influenced by and change over geologic time in the Transantarctic Mountains, Antarctica.
25	Michael Schleh	Alpha cell antigen presentation drives CD8+ T cell infiltration in the aging pancreas and is reversed by calorie restriction
26	Ronald McMillan	Chemerin Contributes to Sodium Induced Cardiometabolic Disease and Salt-Sensitive Hypertension in Humans
27	Salah Alahwany	Safety and Outcomes of Ventricular Tachycardia Ablation in Pediatric Arrhythmogenic Right Ventricular Cardiomyopathy
28	Jayden Lee	Social cognitive, decision-making, and neuroimaging markers of financial vulnerability in patients with dementia
29	Withdrawn	
30	Michael Schleh	Alpha cell antigen presentation drives CD8+ T cell infiltration in the aging pancreas and is reversed by calorie restriction

POSTER SESSION SCHEDULE

Morning (M) Session: 10:30 - 11:30 AM (Odd Numbers)
Afternoon (A) Session: 1:15 - 2:00 PM (Even Numbers)

Poster Number	Name	Title
31	Zahrat El Oula	The Has1_ATPase mediated repositioning of Rrp5 regulates assembly of the active rRNA processosome
32	Dalton Nelson	Highly scalable, combinatoric PCR strategy enables augmented panel-based multiplexing for single target detection
33	Carlos Tellet Cabiya	Assessing Cibenzoline as an Alternative for Catecholaminergic Polymorphic Ventricular Tachycardia
34	Withdrawn	
35	Milene Fontes	The Role of GPNMB in Infection-Mediated Endothelial Dysfunction
36	Colleen Walsh	A Systematic Umbrella Review of Firearm-Related Harms Prevention Research
37	Withdrawn	
38	Frank Kiyimba	Human kidney organoids exhibit an intrinsic capacity to biosynthesize cholesterol and estrogen
39	Withdrawn	
40	Indu Bhatia	Structural and biochemical analysis of Zn-dependent metallochaperone function of ZigA from S. aureus

THANK YOU FROM CO-CHAIRS

Ashima Chopra, PhD
VPA Scholarly Advancement Committee
Department of Biochemistry
Vanderbilt University

Rachel Spicer, PhD
Poster and Lightning Talk Committee
Division of Diabetes, Endocrinology,
and Metabolism
Vanderbilt University Medical Center

Welcome to the 2025 Postdoctoral Symposium! It has been a privilege to help organize this event for our vibrant postdoc community – a day to pause from our daily routines, share ideas, and celebrate the breadth of research and creativity that postdocs bring to our institution.

This year, we centered the program around two AI-focused talks to address an ever-growing topic around the globe, and we sincerely hope you find them engaging, relevant, and useful in your own work. Thanks to Dean Matthew Johnson-Roberson and Dr. Charreau Bell for delivering the insightful talks. In addition, this year we surveyed the postdocs for which workshop themes they would benefit the most from. The workshops were arranged according to the majority votes, and we sincerely hope you find them useful. Thanks to Dr. Christine Quinn Trank, Dr. Susan Douglas, and Dr. Heather Bloemhard for organizing engaging sessions catered to the postdocs' interest. Thanks to our Resource Fair presenters for informing postdocs about the wonderful resources available at their disposal across campus.

We want to extend our heartfelt gratitude to Faith Bishop and Annie Evans of the OPA for their support without which the VPA would not be able to organize this symposium! We also want to acknowledge the Symposium Organizing Committee – busy postdocs who made time from their research routines to assist with arranging speakers, managing symposium communication, poster and lightning talks, registrations, and the resource fair. Most importantly, thank you to every postdoc here today – for attending and sharing your science, your stories, and your enthusiasm.

ORGANIZING COMMITTEE 2025

Communications Committee

Alicia Cronin, PhD
Department of Radiology and Radiological Sciences
Vanderbilt University Institute of Imaging Sciences
Vanderbilt University Medical Center

Bilgunay Ilkin Safa, MD
Division of Diabetes, Endocrinology, and Metabolism
Department of Medicine
Vanderbilt University Medical Center

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Hiren Dandia, PhD
Department of Biomedical Engineering
Vanderbilt University

Poster and Lightning Talk Committee

Marium Siddiqui, MD
Department of Surgical Sciences
Vanderbilt University Medical Center

ORGANIZING COMMITTEE 2025

Poster and Lightning Talk Committee

Pooja Mina, PhD
Division of Gastroenterology, Hepatology and Nutrition
Department of Medicine
Vanderbilt University Medical Center

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Seo Yoon Lee, PhD, MPH, RN
Center for Research Development and Scholarship
School of Nursing
Vanderbilt University

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Registration Committee

HyunBin You, PhD, MSN, RN
School of Nursing
Vanderbilt University

Resource Fair Committee

Milene Fontes, PhD
Pediatric Critical Care
Vanderbilt University Medical Center

ORGANIZING COMMITTEE 2025

Supplementary Session Committee

Victoria Stephens, PhD
Division of Infectious Diseases
Department of Medicine
Vanderbilt University Medical Center

Xia Lei, PhD
Department of Pharmacology
Vanderbilt University School of Medicine

OFFICE OF POSTDOCTORAL AFFAIRS

OPA is the driving force behind this symposium - nothing would be done without the help of Faith and Annie. The VPA Symposium Committee thanks them both for all the time and effort they have put forth to make this event possible!

Faith Bishop
Associate Director
Office of Postdoctoral Affairs
Vanderbilt University

Annie Evans
Program and Communications Manager
Office of Postdoctoral Affairs
Vanderbilt University

LIGHTNING TALK ABSTRACTS

Rac1 controls cilia-dependent mechanosensing to enhance kidney tubular differentiation after birth.

Al Borhan Bayazid

Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract:

The nephron is the functional unit of the kidney that consists of a filter, called the glomerulus, and ciliated tubular epithelial cells that reabsorb the primary filtrate. During early development nephrons undergo a complex folding and proximal-distal patterning process. After birth and with rapidly accelerating tubular flow, tubular cells undergo additional differentiation to become mature reabsorbing proximal tubular cells. The signals that specifically initiate postnatal differentiation are largely unknown. Rac1 is a small Rho GTPase and actin cytoskeleton regulator with critical functions in epithelial development. We deleted Rac1 in nephron progenitor cells (Six2+) and unexpectedly found no major kidney developmental phenotype with intact folding, patterning and glomerulus formation. However, postnatally Rac1-null proximal tubular cells rapidly lost their differentiated phenotype, underwent cystic dilatation and the mice died within 4 weeks of birth. We found that despite intact initial differentiation the major defect in newborn Rac1-null tubules was abnormal primary cilia. *In vitro,* Rac1-null tubular cells showed impaired ciliogenesis after serum starvation and failed to further differentiate upon application of fluid shear stress, an effect that could be recapitulated with cilia-deficient (Ift88-Knock Down) cells. Rac1-null cells had excessive actomyosin activation resulting in impaired ciliogenesis. Direct myosin inhibition in Rac1-null cells reversed the cilia defect and rescued fluid shear stress-induced tubular differentiation. Collectively, our findings demonstrate that Rac1 is dispensable for early nephron specification but is essential for postnatal tubular differentiation via cilia-dependent sensing of apical mechanical stress.

The Role of GPNMB in Infection-Mediated Endothelial Dysfunction

Milene Tavares Fontes1, Sourav Panja1, Hyehun Choi1, Hong-Ngan Nguyen1, Fred S. Lamb1, Ryan Stark1.
1Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN

Sepsis, a life-threatening condition caused by a dysregulated immune response to infection, remains a leading cause of death worldwide. A key feature of sepsis is vascular dysfunction, marked by endothelial cell (EC) activation, disrupted vascular tone, and microvascular leakage—all of which greatly contribute to organ failure. Despite extensive research, effective treatments targeting endothelial dysfunction in sepsis continue to be lacking. Nonmetastatic melanoma glycoprotein B (GPNMB), a transmembrane glycoprotein found on endothelial and immune cells, has been linked to the regulation of inflammation, metabolism, and tissue repair. However, its role in sepsis-induced vascular dysfunction is not well understood. To explore the role of GPNMB in endothelial inflammation during infection, we conducted experiments using human microvascular endothelial cells (HMVECs) with GPNMB knockdown (siGPNMB) and exposed them to heat-killed *Escherichia coli* (HKEC), a common sepsis pathogen. Additionally, we utilized a polymicrobial sepsis model (Enriched Cecal Suspension) to induce sepsis in DBA/2J (KO) and DBA/2J-Gpnmb+ (WT) mice. Under basal conditions, siGPNMB cells exhibited increased transendothelial electrical resistance, indicating changes in pathways related to barrier function. However, upon HKEC exposure, siGPNMB cells showed greater barrier dysfunction compared to controls. Furthermore, siGPNMB cells displayed impaired viability, proliferation, and migration after HKEC exposure. Metabolic assessments revealed that HKEC exposure decreased oxygen consumption and increased extracellular acidification in control cells, but these metabolic shifts were absent in siGPNMB cells, suggesting a critical role for GPNMB in metabolic reprogramming during infection. In vivo, six hours after sepsis induction, both WT and KO Sepsis mice exhibited reduced blood pressure compared to SHAM mice, with KO mice showing a more pronounced reduction. Although the mice's blood pressure returned to normal within 72 hours, we observed changes in vascular reactivity. Phenylephrine-induced contraction was significantly reduced in septic animals, with KO mice exhibiting greater impairment. And endothelium-dependent relaxation in response to acetylcholine was enhanced in septic KO mice, indicating dysregulated vascular tone. Also, cytokine analysis at 72 hours revealed elevated pro-inflammatory cytokine levels in SHAM KO mice compared to SHAM WT mice (TNFα, IL-6 and IFNγ). Following sepsis induction, cytokine levels increased significantly in both groups, with KO mice showing a more intense inflammatory response. These results suggest that GPNMB deficiency exacerbates vascular inflammation and disrupts immune homeostasis during sepsis. In summary, our study highlights the crucial role of GPNMB in maintaining vascular stability during infection. The absence of GPNMB impairs endothelial barrier integrity, metabolic reprogramming, and vascular reactivity, while amplifying inflammatory responses in a polymicrobial sepsis model. These findings provide valuable insights into the mechanisms underlying sepsis-induced vascular dysfunction and identify GPNMB as a potential therapeutic target for mitigating endothelial damage in sepsis.

Mechanistic basis of biphasic DNA replication fork progression in unperturbed S phase

Abstract

Somatic cells exhibit differential DNA fork velocities along the DNA synthesis phase of cell cycle. We interrogated the mechanism and significance of biphasic fork dynamics in the present study. We found that the slowing of fork speed in Early S phase (ES) is not associated with high transcription rates, chromatin compaction levels or nucleotide availability. Instead, the higher number of replication origins fired during ES increases the topological stress on the DNA, ahead and behind the advancing replication fork. This in turn increases the demand for Topoisomerase 2 alpha (Top2A) to resolve the topological strain for DNA synthesis to continue unimpeded. However, the TOP2A availability is not commiserate with the number of origins fired which thus leads to fork uncoupling, slower fork speed and basal ATR-CHK1 activation in ES. Overexpressing TOP2A restores the fork speed in ES even when the origin firing is pathologically induced by oncogene expression. Furthermore, we found that overexpression of TOP2A alters the replication timing or the temporal order of genome duplication. Upregulation of TOP2A in certain cancers may explain the sustained proliferation observed in them. Collectively, our findings reveal that TOP2A levels are key regulators of fork dynamics and genome integrity maintenance.

Social Network Profiles and Self-Perceptions of Aging among LGBTQ+ Older Adults

Anyah Prasad

Background and Objectives: Time is a fundamental resource. In later life, people become increasingly aware of the passage of time and the age-related changes in their bodies and surroundings, a phenomenon referred to as self-perceptions of aging (SPA). People with positive SPA tend to be healthier and live longer than people with negative SPA. There is preliminary evidence that LGBTQ+ older adults have more negative SPA than their heterosexual counterparts, reflecting the well-documented health disparities. Since there is emerging evidence of the importance of social relationships for SPA, this study examines how LGBTQ+ older adults' social relationships, shaped by constraints (prejudice, lack of marriage/adoption rights, family estrangement) and opportunities (community, affinity), influence their SPA.
Research Design and Methods: We use data from wave 1 of the LGBTQ+ Social Networks, Aging and Policy Study (QSNAPS), a sample of 1256 LGBTQ+ individuals aged between 50 and 76 from the US South. To capture the rich and multidimensional nature of social relationships, an ego-centric approach was used to collect information not only about the respondent but also about each member of their social networks. We used Latent Profile Analysis (LPA) to group the respondents based on shared network characteristics most pertinent to their life course, i.e., if they are married/partnered, have children, social network size, the percentage of their networks composed of kin, friend, or weak ties, and the percentage of ties who are also LGBTQ+, 50 years or older and that the respondent is out to about their identity. We then compared how respondents in the network profiles differed in their SPA measured as subjective age, age anxiety, and present and future self-rated health (SRH).
Results: The fit statistics of the LPA (AIC, BIC, entropy, and Lo-Mendell-Rubin Likelihood Ratio Test) show that a four-category model is the best-fitting model and conceptually the most meaningful. The mean probability of respondents being assigned to their respective categories is greater than 0.8, suggesting robust classification. The four groups are closeted, kin-centered, friend-centered, and diverse social networks named based on their defining network characteristic. In the first group, respondents disclosed their identity to only 25% of their network ties compared to 90% in the other groups. The closeted group had the smallest network size and was least likely to be married/partnered. Friend-centered group respondents were most likely to be married, childless, and have networks that are most homophilous by age and LGBTQ+ status. Diverse networks are the largest and most balanced. Compared to the closeted and kin-centered groups, respondents in friend-centered and diverse groups felt about three more years younger than their chronological age and had significantly better SRH. Closeted group expressed the most anxiety about aging compared to the other groups, but the four groups did not differ in the future SRH.
Discussion and Implications: LGBTQ+ respondents with the most restrictive social networks, as a result of restrictive policies, have more negative SPA, but those who showed resilience in overcoming the challenges and forming robust social networks have better SPA. Screening social networks to identify those at most risk and developing network-based interventions to improve SPA can be helpful in enhancing LGBTQ+ older adults' health and ensuring health equity.

Table – Regression models for self-perceptions of aging.

	Felt Age	Age Anxiety	SRH	FSRH
Network Profiles (Closeted – ref)				
Kin-Focused	-0.68	-0.57*	0.02	0.03
Friend-Focused	-3.13*	-0.57*	0.19†	0.24
Diverse	-3.41**	-0.87***	0.23**	0.17
Age	-0.38***	-0.04**	0.02***	0.01
Race-Ethnicity (Non-Hispanic White – ref)				
Non-Hispanic Black	-1.88	-0.82***	0.05	0.57**
Other Race-Ethnicity	-1.34	0.04	0.05	0.13
Gender-Sexuality (Gay Men – ref)				
Lesbian Women	1.45†	-0.41**	-0.21***	-0.32**
Bisexual Men	-2.93	-0.67	-0.12	0.12
Bisexual Women	1.23	-0.35	-0.19	-0.63**
Trans Masculine	-0.37	-0.26	-0.22	-0.41
Trans Feminine	-0.09	0.10	-0.26*	-0.78**
Marital Status (Married/Partnered – ref)				
Widowed/Separated/Divorced	-0.93	0.09	-0.07	-0.15
Never Married	-1.28	0.06	-0.14*	-0.28*
Education (Less than College – ref)				
College degree	-1.47	0.07	0.14*	0.32*
Graduate	-0.69	-0.07	0.14*	0.41**
Income (≤ 44,999 – ref)				
45,000 – 74,999	0.23	0.0	0.15**	0.09
75,000 – 124,999	-0.69	-0.39*	0.24***	0.15
≥ 125,000	0.41	-0.06	0.44***	0.34
Retired	0.50	-0.85***	-0.05	-0.19
# Chronic Conditions	1.25***	0.32***	-0.29***	-0.55***
R^2	5.32%	10.78%	27.27%	20.95%

Notes: SRH – Self-Rated Health; FSRH – Future Self-Rated Health
*$p < .05$ **$p < .01$ ***$p < .001$

The cell adhesion protein ALCAM controls the cargo composition of EVs

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ALCAM is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily that regulates the dynamic turnover of adhesions and contributes to the control of cell motility. It is expressed in various cell types, including bladder epithelium. Given the critical emerging roles of extracellular vesicles (EVs) in regulating cancer cell migration and metastasis, we asked whether ALCAM might impact EV biogenesis, composition, or function to control bladder tumor cells. To study the effects of ALCAM on cancer cells, we generated an ALCAM-deficient UMUC3 bladder tumor cell line using CRISPR-Cas9. EVs were isolated from control and ALCAM knockout cell culture supernatants by size exclusion chromatography followed by ultracentrifugation and characterized by nanoparticle tracking (ZetaView), western blot, flow cytometry with dimensional reduction analysis of single EVs after staining with Di8-ANEPPs lipid dye (“EV fingerprinting”), and proteomics. Nanoparticle tracking identified an increase in small EVs produced from ALCAM-deficient cells. EV fingerprinting identified a select enrichment of subpopulations of EVs in these cells. Proteomics of EVs demonstrated abundant cargos related to cell-cell adhesion, cell migration, ECM-receptor interaction, focal adhesion, and signaling pathways in cancer. This analysis identified an increase in alpha 2 integrin (ITGα2) and a decrease in alpha 3 integrin (ITGα3) in EVs from ALCAM-deficient cells, which was confirmed by western blot and single vesicle flow cytometry. Consistent with these changes, we detected higher levels of laminin in wild-type EVs, which contained higher levels of ITGα3, a receptor for this extracellular matrix protein. Together, our data indicate that ALCAM affects the protein composition of the EVs secreted from the UMUC3 cancer cell line. Future studies will explore the functional impacts of these EVs on bladder cancer cell behavior.

Need for a Roadmap: ICU Survivor Insights on Post-Discharge Recovery

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Introduction: Many critical illness survivors experience post-intensive care syndrome (PICS), but inadequate discharge education leaves patients and caregivers unprepared for the complexities of long-term recovery. This study explored what ICU survivors wish they had known before hospital discharge about recovery from critical illness.

METHODS: We conducted a thematic analysis of open-ended responses to the question "What specifically, if anything, do you wish you would have been told before leaving the hospital about the recovery from critical illness, the possible impairments, and challenges?" from a single-site online survey of ICU survivors (October 2024-March 2025). A multidisciplinary team inductively coded responses and refined themes through iterative consensus-building.

RESULTS: Of 146 survey respondents (9% response rate), 125 provided responses and were included in the qualitative analysis. ICU survivors were middle-aged (mean age = 53), White (93%), and 50% male. Three major themes emerged. **(1) Need for symptom and recovery education.** Patients shared a wide range of post-ICU challenges, including persistent PICS symptoms, emphasizing the need for timely, clear, and individualized information. Many highlighted gaps in education and a desire to include PICS-related and medical condition-related communication in care planning. **(2) Need for health system navigation.** Patients experienced fragmented care transitions and expressed a strong desire for clear guidance with concrete referrals and accessible resources in navigating the healthcare system after ICU discharge. Many hoped for better communication about the expected timeline for recovery and when important information would be shared. **(3) Need for emotional and social support.** Patients underscored the importance of emotional and social support in their recovery, expressing a desire for greater inclusion of family members. In reflecting on their recovery, many patients described how deeply they relied on family caregivers for emotional reassurance, daily assistance, and motivation. **(4) Finding strength through preparedness, gratitude, and connection.** Some ICU survivors described drawing strength from feeling prepared, supported, and emotionally grounded as they navigated recovery. These individuals expressed gratitude toward their healthcare teams and families, and, for some, these reflections fostered a renewed sense of purpose and helped redefine personal goals after critical illness.

CONCLUSIONS: Findings underscore the importance of providing timely, tailored information and setting realistic expectations to support ICU survivors during recovery. These insights can guide the development of structured, patient- and family-centered strategies in clinical practice and inform future research to optimize post-ICU care delivery.

4-Phenylbutyrate Treatment for Pathologic Changes in GABAergic Neurotransmission in *Slc6a1*$^{+/S295L}$ and *Gabrg2*$^{+/Q390X}$ Mouse Models of Genetic Epilepsy

Kirill Zavalin. Alok Karkare, Karishma Randhave, Wanyi Su, Luke Wedemeyer, Jing-Qiong Kang

Rationale

A significant need exists for development of new precision therapy for genetic epilepsies (GEs), particularly severe encephalopathies, where co-morbidities and often seizures are resistant to treatment with canonical anti-seizure drugs. In recent years, we found that chemical chaperone 4-phenyl butyrate (PBA) treatment mitigated seizures and addressed multiple aspects of underlying pathology in two monogenetic GEs with mutations in vital constituents of GABAergic neurotransmission: 1) developmental and epileptic encephalopathy associated with S295L mutation in *SLC6A1*, encoding GABA transporter 1, and 2) Dravet syndrome associated with Q390X mutation in *GABRG2*, encoding ɣ2 subunit of the GABAA receptor.

We hypothesize that PBA acts in a targeted fashion to reverse GABAergic dysfunction in these disorders, making it an excellent candidate for novel precision therapy that is applicable to multiple GEs. To test this hypothesis, we characterized GABAergic dysfunction in the *Slc6a1*$^{+/S295L}$ and *Gabrg2*$^{+/Q390X}$ mouse models, and evaluated if PBA treatment can restore this pathology.

Methods

We measured GABAergic neurotransmission using patch clamp electrophysiology in cortical pyramidal neurons in presence of AP5 and NBQX in *ex vivo* brain slices from adult 2-4 month old *Slc6a1*$^{+/S295L}$ and *Gabrg2*$^{+/Q390X}$ mice and wildtype siblings. Additionally, we evaluated neuronal activity on a population level in *Gabrg2*$^{+/Q390X}$ mice using intracellular calcium indicator GCaMP8f, introduced by injection of pGP-AAV-syn-jGCaMP8f-WPRE virus at a titer ≥ 1×10^{13} vg/mL 3-5 weeks before experiment. We evaluated neuronal responses to increased stimulation with 1 Hz stimulation in layer 4 or washon of potassium channel blocker 4-aminopyridine. PBA treatment included a 100 mg/kg/day 7-day intraperitoneal or 28-day oral administration with recording on the last day.

Results

We found that evoked and spontaneous inhibitory postsynaptic currents (eIPSCs and sIPSCs) are longer in *Slc6a1*$^{+/S295L}$ mice. Mice treated with the shorter 7-day treatment still showed these deficits; those treated with the longer 28-day treatment showed a restoration of sIPSC decay closer to wildtype levels but still had prolonged decay of eIPSCs. Direct PBA washon did not affect eIPSC/sIPSC kinetics.

In *Gabrg2*$^{+/Q390X}$ mice, we found that miniature IPSCs are smaller in amplitude, which persisted after the 7-day treatment with PBA. Preliminary data using calcium imaging indicate that neuronal activity in *Gabrg2*$^{+/Q390X}$ mice is similar to wildtype at baseline, but increases with 4-aminopyridine application or stimulation.

Conclusions

Prolongation of synaptic currents in *Slc6a1*$^{+/S295L}$ mice is consistent with role of GAT-1 as the primary mechanism of uptake of extrasynaptic GABA after its release. Previously, we reported that 7-day PBA treatment leads to a significant reduction of seizures; we did not observe a matching restoration of IPSCs with PBA washon or 7-day treatment, indicating potentially different mechanisms for these phenomena. The longer 28-day treatment did restore sIPSC kinetics, indicating that long-term treatment can address the synaptic deficits.

In *Gabrg2*+/Q390X mice, reduction in mIPSC amplitude matches prior reports. Previously, we showed that the 7-day PBA treatment significantly reduced the seizure burden in these mice; however, we did not see a significant restoration of mIPSC amplitude. Our ongoing efforts in this model are investigating hyperexcitability of neurons on the population level.

POSTER ABSTRACTS

The Effect of Ansa Cervicalis Stimulation on Velopharyngeal Cross-sectional Area in Patients with Obstructive Sleep Apnea

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Introduction and Objectives: Obstructive sleep apnea (OSA) is characterized by recurrent pharyngeal obstruction during sleep. Ansa cervicalis stimulation (ACS) is proposed as an alternative therapeutic neurostimulation mechanism for maintaining airway patency, but it is currently unknown whether ACS dilates or stiffens the pharynx. The effect of ACS was investigated in this study by plotting velopharyngeal CSA across a range of intraluminal pressures.

Methods: Pharyngeal intraluminal pressure and cross-sectional area (CSA) were assessed in twenty-one patients with moderate-to-severe OSA during drug-induced sleep endoscopy (DISE). Continuous positive airway pressure (CPAP) was applied by nasal mask. ACS was applied by fine-wire percutaneous electrodes and changes in CSA were measured from endoscopy at end-expiration for intraluminal pressures ranging from non-flow-limited inspirations (POPEN) to atmospheric pressure or apneic inspirations (PCRIT). Pressure-area curves were plotted using a linear mixed effects model.

Results: ACS generally increased mean CSA 0.64 cm2 [0.40, 0.88] cm2; $p<0.05$). ACS decreased PCRIT by 2.5 cmH2O [1.6, 3.4], and decreased POPEN by 1.8 cmH2O [0.3, 3.6] ($p<0.05$). The slope of CSA response shifted left but did not change significantly in a linear mixed effects model ($p=0.324$).

Conclusions: ACS increased velopharyngeal CSA over a range of airway pressures, but it did not alter the slope of CSA response to CPAP. The findings suggest that ACS primarily dilated the velopharyngeal lumen by reducing surrounding tissue pressures rather than stiffening the airway. ACS may have different local effects on other pharyngeal structures. Analyses are continuing across an expanded patient cohort.

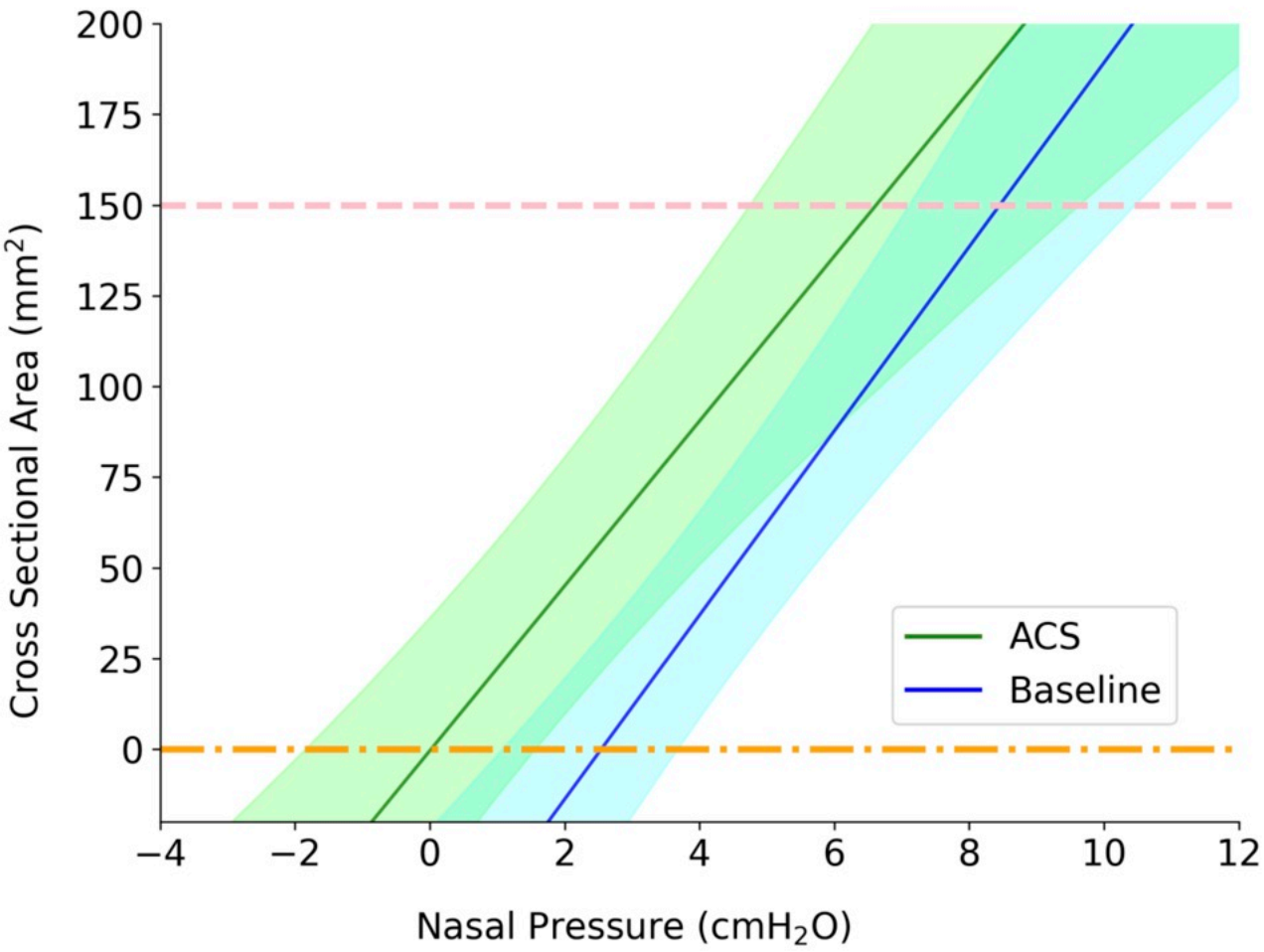

Figure 1. A linear mixed effects model plotting pharyngeal cross-sectional area (CSA) against nasal continuous positive airway pressure (CPAP). The slope of CSA response did not change significantly in a linear mixed effects model (p=0.324).

Zoe Petros

Proteolysis targeting chimeras (PROTACs) have emerged as a promising strategy for cancer therapy in the field of drug discovery. PROTACs are heterobifunctional small molecules that bind to both a target protein and an E3 ubiquitin ligase, thus facilitating degradation of the target protein of interest. Benefits of PROTACs as an alternative therapeutic strategy include the ability to target inaccessible proteins, the regulation of target protein signaling pathways, and overcoming drug resistance in certain types of cancer. There are more than 600 known E3 ligases in the human genome, but current PROTAC technology has been limited to the use of CRBN, VHL, XIAP, and MDM2. Therefore, the discovery of novel ligands for different E3 ligases could further improve current PROTAC technology. An application that our research group has focused on is exploring the possibility of tissue selective E3 ligases that are overexpressed in cancer cells compared to normal tissue to design tissue selective PROTACs for a target of interest. We have observed that protein levels of the E3 ligase KLHL12 are low in normal tissue and high in cancer cells. Using structure-activity relationship (SAR) by nuclear magnetic resonance (NMR), we identified hits that bound to the KLHL12 E3 ligase, which were then optimized to bind in the range of 10-100 nM K_d by SPR. We then generated KLHL12 based PROTACS that target BRD4 and Bcl-xL using thalidomide and A-115463 derivatives, respectively. PROTAC activity was optimized by measuring protein target degradation in HT29 cells by an in-cell western experiment where our most potent degrader had an average DC_{50} of 250 nM and achieved 90% degradation. Mechanism studies were carried out to verify that the PROTACs behaved in both a proteasome and target dependent manner. Future studies will support further characterization of KLHL12 by investigating its expression patterns across various cancer tissues, its functional essentiality in cells, and its involvement in protein-protein interactions.

Comparison of Adherence to Self-Care Behaviors between Unemployed and Employed Black Informal Caregivers

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Background: One in five Americans provides informal caregiving and support to their family members with acute or chronic illnesses. Although these caregivers contribute to improving the health outcomes of sick family members, they experience a significant caregiving burden, leading to adverse physical and mental health outcomes. Many caregivers often face challenges in balancing their dual roles as workers and informal caregivers at home, and some leave the workforce due to caregiving demands. Engaging in health promoting self-care is critical to preventing poor health outcomes, yet we have a limited understanding of how employment status relates to caregivers' self-care. Furthermore, there is a lack of knowledge in self-care among Black caregivers, who report higher unmet needs than other racial groups. Thus, the specific aim in this study was to examine differences in engagement in self-care behaviors between employed and unemployed Black informal caregivers.

Method: In this cross-sectional study, Black caregivers participated in a survey from June to August 2024 in community libraries. We assessed adherence to self-care behaviors using the Medical Outcome Study Specific Adherence Behavior Scale to capture adherence to 12 self-care practices, including adherence to physical activity, medication, smoking cessation, limited alcohol consumption, healthy diet, and stress management. Participants responded on a 6-point Likert Scale (0= none of the time to 5 = all the time). Item scores were summed up to create an overall self-care adherence score (range: 0 -60), with higher scores indicating greater adherence to health behaviors. Employment status was assessed using a single item and dichotomized into employed (full-time or part-time) versus unemployed (housemakers, retired, unemployed, and other). Group differences were examined using independent sample two-tailed t-tests and Chi-square tests.

Results: Of 56 Black caregiver participants (mean age= 55±14.2), females consisted of 83.9%. 73.2% of participants were single, divorced, or widowed. 35.7% of participants were employed. Employed caregivers were significantly younger (M= 45.1±14.7) than unemployed caregivers (M = 60.5±10.5, $p<0.001$). There were no significant differences in sex and educational status. The overall self-care adherence was significantly lower in employed caregivers (M = 23.45±14.71) compared with unemployed caregivers (M = 33.8±13.7, $p=0.01$). When examining adherence to individual self-care behaviors, the employed caregivers reported significantly lower scores than unemployed caregivers for low-sat/trans-fat diet, low-fat diet, low-sodium diet, whole-grain diet, low/non-fat dairy consumption, and beans/seeds/nuts consumption (all $p<0.05$).

Conclusion: Our study revealed that employed caregivers had greater challenges in self-care, particularly in adherence to healthy diet practice. Identifying barriers to healthy diet adherence

and developing practical strategies to support self-care behaviors in this employed Black caregivers population is essential.

Word count 421/Max 500

Ingestive behaviors and energy homeostasis during and after GLP-1R agonist treatment in mice

Harsh Shah,Ph.D., Julio E. Ayala,Ph.D.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) promote weight loss by reducing food intake. However, the effects of these agents on ingestive behavior and energy expenditure during and after treatment remain poorly undefined in mice. Notably, conventional housing temperature for mice (22°C) is well below their thermoneutral zone (29°C), and this may impact the translatability of findings due to physiological adaptations required for thermoregulation. To address this, we investigated changes in energy homeostasis and ingestive behaviors in diet-induced obese mice during and after chronic treatment with the GLP-1RA semaglutide under both room temperature (RT) and thermoneutral (TN) conditions.

Two independent cohorts of male mice were fed a 60% high-fat diet for 8–10 weeks to induce obesity before being transferred to metabolic chambers. One cohort of mice remained at RT, while the other was maintained at TN. Following 3 to 6 days of acclimatization period in metabolic chambers, mice were treated with either saline or semaglutide subcutaneously (n=7-8 per group, 60 μg/kg/day) for 21 days, followed by a 7-day washout period. Throughout the study, body weight, food intake, meal patterns, and energy expenditure were monitored.

When comparing saline-treated groups at both temperatures, mice housed at RT exhibited approximately 24% higher food intake and 36% greater energy expenditure compared to those at TN. Notably, mice maintained at RT consumed larger but fewer meals, with longer meal durations compared to mice at TN. Despite these differences, semaglutide-treated mice lost comparable amounts of body weight at both temperatures. This weight loss followed a triphasic pattern, with an initial rapid weight loss followed by a gradual decline that eventually plateaued. During rapid weight loss, reduced food intake was driven by decreases in both meal size and frequency at both temperatures. During the gradual weight loss period, food intake increased due to an increase in meal numbers at both RT and TN. As weight loss plateaued, meal size slightly increased at both RT and TN. Meal frequency increased to levels above the saline-treated group only in mice at RT. Weight-adjusted energy expenditure remains slightly elevated during the treatment period at both temperatures. Upon treatment cessation, mice rapidly regained weight as food intake rebounded, primarily due to an increase in meal size.

These findings reveal key physiological adaptations that occur due to temperature differences in mice during and after GLP-1RA treatment. Future studies will investigate neural mechanisms underlying semaglutide-induced changes in ingestive behavior in different weight loss phases.

Multimessenger and Multiband prospects for binary neutron stars from the Moon

Anjali Yelikar

August 24, 2025

Gravitational waves from coalescing binary neutron stars (BNS) offer crucial insights into matter under extreme conditions of gravity and density, highlighted by the landmark event GW170817. Despite the availability of advanced waveform models for parameter estimation, uncertainties in modeling can introduce biases in recovering source properties, impacting our understanding of the neutron star population and the equation of state (EoS). Furthermore, with the enhanced sensitivity of current-generation detectors, such as LIGO and Virgo, and future developments like Cosmic Explorer and Lunar gravitational wave observatories, we anticipate substantial improvements in the observation and localization of BNS events. In this study, we perform a systematic comparison of BNS observations and the equation of state with detector networks that include Earth- based and Moon-based gravitational wave detectors. Our work paves the way for a novel intersection of gravitational wave astronomy with NASA's Lunar exploration program, Artemis.

Alexander Kwiatkowski

Introduction: Glioblastoma (GBM) is a rare form of brain cancer with over 13,000 new cases each year and a dismal outlook for patients who face a mean survival time of 12-18 months post-diagnosis. The current standard of care – comprising surgical resection followed by radiation and chemotherapy – has not advanced significantly over the past 20 years, creating a need for new therapies. To this end, leveraging pattern recognition receptor (PRR) activation to elicit strong innate immune responses shows promise for cancer immunotherapy. Retinoic acid inducible gene I (RIG-I) is one such PRR, and higher levels of RIG-I are associated with improved survival outcomes for GBM patients. RIG-I recognizes short double-stranded RNA with a triphosphate (3p) group on the 5' end (3pRNA), and RIG-I activation stimulates trigger antitumor immunity. Despite their promise for cancer immunotherapy, the clinical utility of 3pRNA RIG-I agonists is currently limited by significant drug delivery barriers, including poor intracellular uptake and an inability to reach the cytosol to bind RIG-I. To realize the promise of RIG-I, we will use **RIG-I activating nanoparticles (RANs)** to treat a mouse model of GBM.

Methods and Materials: Di-block copolymer consisted of a first block of 10 kDa methoxy-polyethylene glycol (mPEG) and a second block of PDSMA poly[(DMAEMA-c-(BMA)) (PDB). The PDB block is pH responsive and complexes with the RNA. To form micelles, the di-block copolymer was dissolved in ethanol then diluted with sterile-filtered citrate buffer (pH=4.2). RNA was complexed to NPs for 45 minutes at room temperature, then agarose gel electrophoresis verified RNA loading and dynamic light scatter (DLS) quantified size. Mouse bone marrow-derived macrophages (BMDMs) and dendritic cells (BMDCs) were treated with RANs, 24 hours later, supernatants were collected for ELISA.

Mice were inoculated with 1,000,000 GL261 or CT2A cells on the right flank. When tumors reached ~50 mm^3, mice were treated intratumorally with RANs, with additional injections on days 3 and 6 post treatment initiation. Orthotopic tumors were engrafted in the caudoputamen using 200,000 CT2A-luciferase cells. Mice were treated intratumorally with RANs 11 and 18 days post engraftment using the same injection coordinates as engraftment.

Results, Discussion, Conclusions: DLS displayed that RANs were ~70 nm in diameter (Fig. 1A), and gel electrophoresis confirmed successful RNA complexation (Fig. 1B). We show that both BMDMs and BMDCs treated with RANs were activated to produce pro-inflammatory interferon and increase antigen presentation compared to cells treated to cRANs (Fig. 1C-F). cRANs contain the same stem loop without the 5' triphosphate to activate RIG-I. RANs significantly delayed tumor growth and prolonged survival in both GL261 and CT2A flank tumors (Fig. 1G-H). Additionally, RANs can delay the growth of **orthotopic** CT2A-Luc tumors with an extension of median survival time by 9 days compared to cRANs (Fig. 1I). Overall, RANs increase in pro-inflammatory gene expression and delay tumor growth, showing preclinical promise to combat a deadly cancer.

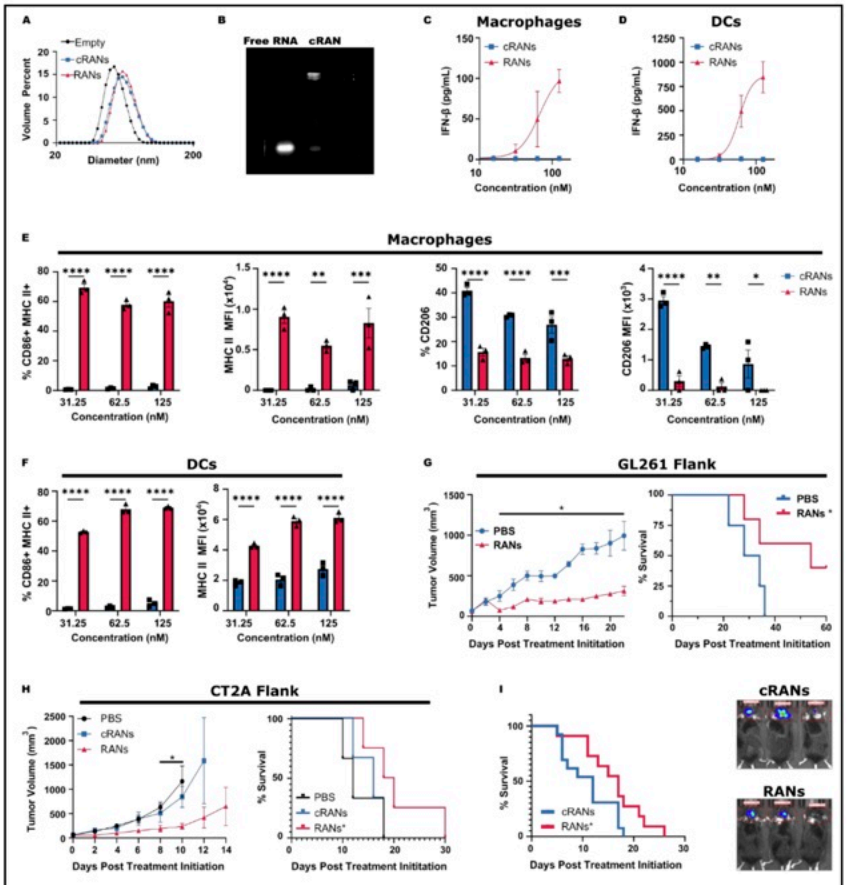


Figure 1. RANs are effective in treating GBM. A) Determination of NP size via DLS. B) Evaluation of RNA complexation to NPs via agarose gel electrophoresis. Quantification of Type I IFN produced by C) BMDMs and D) BMDCs in response to RANs. E) Expression of activation (CD86 and MHC II) and suppression (CD206) markers by BMDMs. F) Analysis of pro-inflammatory signaling by BMDCs. n=3 per group. Tumor growth and Kaplan-Meier survival curves following intertumoral treatment of flank more immunogenic G) GL261 and less immunogenic H) CT2A tumors on days 0, 3 and 6. n-7-10 per group. I) Kaplan-Meier survival curves following intratumoral treatment of orthotopic GBM tumors on day 11 and 18 post engraftment. n=8-10 per group and data is the combination of two pooled experiments. P values determined by one-way ANOVA with Tukey's post-hoc test and survival statistics were determined using a Kaplan-Meier curve and the Log-rank (Mantel-Cox) test. * represents p<0.05, ** represents p<0.01, *** represents p<0.001, and **** represents p> 0.0001.

High-Throughput Selection of Conformation-Specific Nanobodies Targeting EGFR

R. M. Madhushi N. Ratnayake, Yongjian Huang, John Kuriyan

Abstract

Nanobodies, the single-domain antigen-binding fragments derived from camelid antibodies, have emerged as powerful molecular tools for stabilizing and interrogating dynamic protein conformations. Their small size, high solubility, and capacity to recognize transient epitopes make them ideally suited for capturing proteins in specific functional states—an essential requirement for structural and mechanistic studies of conformationally flexible targets such as membrane proteins. However, conventional nanobody discovery relies on camelid immunization, a slow, costly, and resource-intensive process that can limit accessibility and throughput. To circumvent these challenges, a fully synthetic nanobody library displayed on the surface of *Saccharomyces cerevisiae* was developed by McMahon et al., enabling rapid, entirely *in vitro* selection of conformation-specific nanobodies without the need for animal immunization.

In this work, we apply this yeast surface display platform to discover and characterize nanobodies targeting the Epidermal Growth Factor Receptor (EGFR), a receptor tyrosine kinase central to cell proliferation, survival, and oncogenesis. The synthetic nanobody library was screened using a sequential selection strategy combining magnetic-activated cell sorting (MACS) and fluorescence-activated cell sorting (FACS). MACS provided rapid enrichment of EGFR-binding clones from the naïve library, while FACS enabled high-resolution discrimination and isolation of yeast displaying nanobodies that preferentially bound specific EGFR conformations. Over multiple selection rounds, EGFR concentrations were systematically decreased to favor recovery of higher-affinity binders while depleting the library for nanobody clones that bind to unintended conformations of EGFR. This approach yielded several candidate nanobodies with promising conformation-specific binding profiles for downstream characterization.

Following isolation, nanobody genes were cloned into bacterial expression vectors, expressed, and purified for cellular and biophysical assays. Initial binding validation using Biolayer Interferometry (BLI) confirmed specific EGFR recognition, setting the stage for comprehensive kinetic and functional studies. To assess biological relevance, selected nanobodies will be tested in cell-based assays to evaluate their capabilities in both ligand-dependent and ligand-independent contexts, which will aid in classifying nanobody function. Finally, structural characterization of EGFR–nanobody complexes will be pursued through cryo-electron microscopy. High-resolution structural data will elucidate the molecular basis of nanobody–EGFR recognition, inform epitope mapping, and guide subsequent engineering efforts to improve affinity, stability, and potential therapeutic utility.

Together, this study demonstrates the utility of a synthetic yeast display platform for the rapid discovery of EGFR-binding nanobodies and establishes a streamlined pipeline from selection to structural and functional characterization. Our findings lay the groundwork for the development of nanobody-based tools for mechanistic studies and potential therapeutic intervention in EGFR-driven diseases.

(418 words)

Anastasia Varanko

Immune checkpoint blockade therapies hold transformative potential for cancer treatment but face limited efficacy in many patients due to an immunosuppressive tumor microenvironment (TME). Regulatory T cells (Tregs) are key mediators of this suppression, dampening cytotoxic T lymphocyte activity and enabling immune evasion. Although Treg-targeting therapies, such as CTLA4 inhibitors, show promise, their use is constrained by systemic toxicity, underscoring the need for innovative and selective approaches to modulate Treg activity. Our recent findings reveal that activating the Stimulator of Interferon Genes (STING) pathway in Tregs induces a phenotypic shift, reprogramming them toward an anti-tumor, effector T-cell-like state. To harness this phenomenon, we developed a novel protein-based nanocarrier for Treg-specific delivery of STING agonists. This bispecific nanobody-STING agonist conjugate (biNSC) integrates a CTLA4-binding domain for Treg specificity with an albumin-binding domain to enhance pharmacokinetics and circulation time. This dual functionality addresses key pharmacological limitations of STING agonist delivery, enabling targeting and prolonged action within the TME. Our results demonstrate efficient Treg binding, internalization, and controlled drug release, leading to effective STING pathway activation and subsequent phenotypic reprogramming. We demonstrate the potential of this strategy to promote tumor rejection *in vivo*. This innovative, protein biomaterials-based approach offers significant insights into the design of advanced drug delivery systems for precision immunomodulation and represents a promising strategy to boost cancer immunotherapy outcomes.

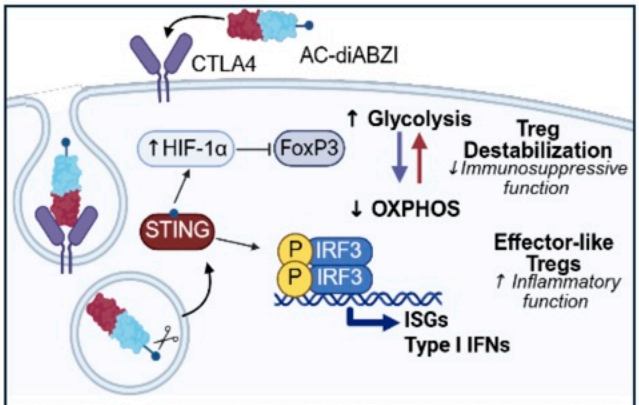


Figure 1. Proposed mode of efficacy. AC-diABZI targets and is internalized by Tregs, activating STING. This metabolically reprograms Tregs, thus suppressing their immunosuppression and inducing the production of inflammatory cytokines.

Limited contribution of sex and sex hormones to regulation of the mouse ductus arteriosus (DA) and human PDA

*Rock C, *Boatwright N, Sorenson C, Israel S, Yarboro MT, Su R, Tolentino C, Paria BC, Clark RH, Shelton EL, Reese, J

*equal contributors

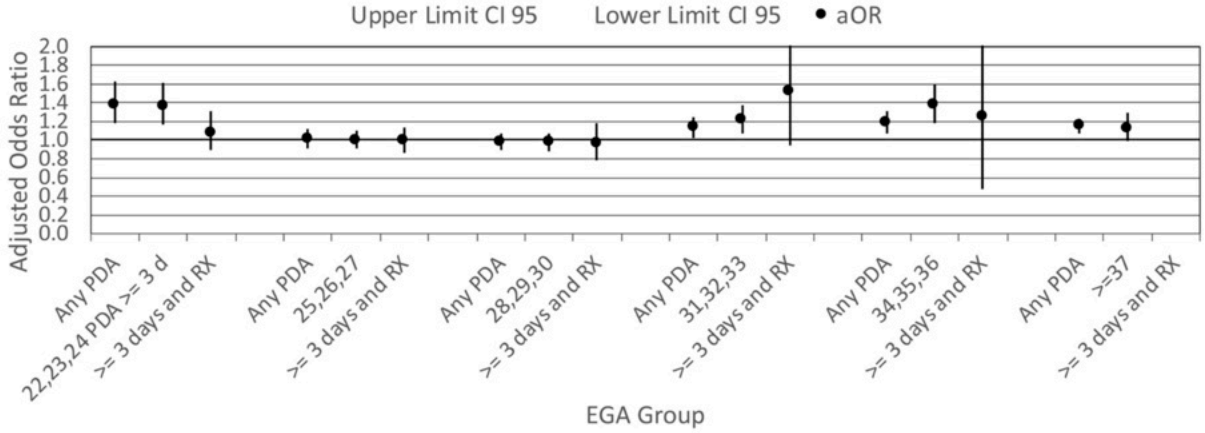
Background: Preterm males have greater risks for multiple neonatal morbidities. Patent ductus arteriosus (PDA) is felt to be more common in male than female preterm infants, however only limited evidence for this exists. The pregnancy hormones estrogen (E2) and progesterone (P4) shift as birth approaches and have vasoactive properties, suggesting potential effects on DA tone. We hypothesized that: 1) E2 and P4 signaling affects DA tone, 2) male and female DAs respond differently to vasoactive stimuli, and 3) male-female PDA predominance is different between early- and late-preterm infants.

Methods: E2 and P4 receptor expression in the mouse DA was examined by RT-PCR. The effects of E2, P4, and vasoconstrictors/dilators on term (e18.5) and preterm (e16.5) fetal DAs were studied by *ex vivo* pressure myography. Published PDA RCTs were re-examined for male-female dimorphism. Data from the Pediatrix clinical data warehouse (CDW) were examined to determine if any report of a PDA occurred more often in male compared to female infants. Data were analyzed by t-test, ANOVA, and multivariate regression logistic regression as appropriate.

Results: Membrane P4 receptors (*Pgrmc1, 2*) were more highly expressed than nuclear receptors (*Pgr* or *Esr1, 2*); *Esr1* was greater in female DAs. E2 induced minor DA relaxation (6%) that was not inhibited by ICI 182,780 (ESR antagonist); P4 induced modest DA relaxation (28%) that was unaffected by RU486 (PGR antagonist). There was no difference in male and female mouse DA responses to constrictors (O2, KCl, U-46619), dilators (PGE2, SNP, distending pressure) or myogenic tone in term or preterm DAs. Of the 62 most-cited PDA RCTs, most did not report sex, or no sex difference was found (n=13). Among 244,109 inborn, non-anomalous infants in the CDW (2016-2019), the reported rates of any PDA were similar across all gestational ages. When evaluated by gestational groups and corrected for EGA, birth weight, and antenatal steroid exposure, the odds of PDA were higher in females than males for the most immature infants (Figure; 1.4 1.2-1.7,<0.0001).

Conclusions: P4 non-genomic signaling via membrane receptors may contribute to fetal DA relaxation prior to birth. Thus, hormone withdrawal may be a mechanism for postnatal DA constriction but requires further study. Contrary to expectation, no difference in DA reactivity exists between male and female mouse DAs at term or preterm gestation. Likewise, only limited data support sexual dimorphism in human preterm PDA, with observational evidence that females, not males, are at marginally higher risk.

Gender Specific Adjusted Odds Ratio (*Female/Male*) For Any Report of a PDA, PDA diagnosed after 3 days and PDA diagnosed after 3 days and medically or surgically treated.
Inborn, cared for at one hospital, no anomalies, and discharged between 2016 and 2019



Title: Overnutrition directly disrupts thyroid hormone biosynthesis, causing hypothyroidism, despite remarkable thyroidal adaptations

Jessica Rampy, Alejandra Paola Torres-Manzo, Kendra Hoffsmith, Rafael Arrojo e Drigo, Huiying Wang, Vivian L. Weiss, and Nancy Carrasco

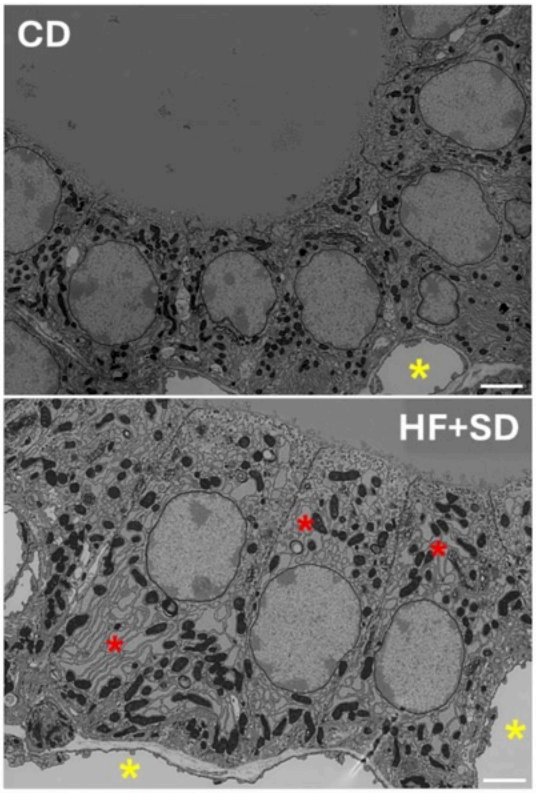


Figure 1. Overnutrition induces major histological and vascular expansion in thyroid cells. Thyroids were processed for electron microscopy. Representative images from a chow diet (CD) mouse (above) and a high-fat + sucrose water diet (HF+SD) mouse (below) are shown. Red asterisks label examples of bloated ER. Yellow asterisks mark microcapillaries. Scale bars = 2.5 µm.

Obesity, which affects >40% of the U.S. population, is increasingly understood as an endocrine disorder. The link between thyroid hormone (TH) dysregulation and obesity is a strong one, and because THs potently increase energy expenditure, thyroid dysfunction (i.e., hypothyroidism) has long been blamed for obesity. Thus, the field has mostly focused on the effects of thyroid status on obesity, but much less is known about obesity's effects on thyroid function. However, emerging evidence suggests that a shift in paradigm, whereby obesity is taken to be the driving factor, is warranted, bolstered by a growing number of studies demonstrating that weight loss improves thyroid function. Thus, ***we hypothesized that overnutrition impairs thyroid function directly***. We tested this hypothesis in male C57Bl/6J mice fed a high-fat diet and sucrose water. Strikingly, overnutrition decreased serum T_4 *after just 7 days*—and progressively induced mild hypothyroidism, with increased thyroid-stimulating hormone (TSH) and goiter, within 3 weeks. Evidence for direct, primary hypothyroidism included the concomitant significant decrease in intrathyroidal T_4 levels, apparent within 10 days. Furthermore, we found increased expression of several ER stress-related proteins, including BiP and p-eIF2α, whereas expression of the TH precursor thyroglobulin (TG) was reduced, despite overexpression of its folding chaperones and high TSH stimulation. These results suggest that overnutrition induced ER stress and impaired protein translation, thereby limiting TG synthesis and impairing downstream TH biosynthesis. Remarkably, though T_4 was low, the thyroid maintained normal serum T_3 by increasing the T_3/T_4 biosynthesis ratio. We also observed pronounced histological and vascular expansion (**Figure 1**), which would promote TH availability. We have seen similar histological changes in preliminary female mouse studies and, notably, in human thyroids, strongly correlating, in the latter case, with BMI. Collectively, our findings show that overnutrition induces mild hypothyroidism, despite the struggling thyroid's best efforts to adapt. Existing data suggest that low T_4 alone can be problematic, particularly in metabolic tissues that rely on serum T_4 to generate intracellular T_3. Fortunately, many of these thyroid symptoms are reversible by weight loss in mice. Even so, the causal role that overnutrition plays in thyroid impairment and decreased TH availability in the pathogenesis of obesity has scarcely begun to be elucidated. Thyroid function has far-reaching effects on whole-body energy balance and thus has untapped therapeutic potential. Our work sheds new light on how overnutrition changes thyroid function and highlights the thyroid's remarkable adaptability.

Title: Mechanistic Investigation of Intracellular Calcium Release Channel RyR2 Inhibitor Cyclic-Oligomeric Depsipeptides as Therapeutic Treatment for Arrhythmogenic Heart Diseases

Tri Do

Sudden cardiac death, often caused by ventricular arrhythmias, is a major health concern in the United States, accounting for 10-20% of adult deaths. Cardiac ryanodine receptor (RyR2) dysfunction is documented in many arrhythmia syndromes, making it a promising target for drug treatment in patients with arrhythmia. Cyclic oligomeric depsipeptides (CODs) represent a distinct structural class of naturally occurring compounds, distinguished by their wide-ranging biological activities. We previously reported that the unnatural form of verticilide (ent-verticilide) inhibits cardiac ryanodine receptor (RyR2) and exhibits antiarrhythmic effects in mice, but its mechanism of action on the RyR2 channel is not known. Here, we performed single-channel recordings in artificial lipid bilayers to elucidate the mechanism of RyR2 modulation by *ent*-verticilide. *ent*-Verticilide reduced RyR2 activity by increasing the RyR2 mean closed time without changing the RyR2 mean open time, suggesting that *ent*-verticilide functions as a closed channel stabilizer. ent-Verticilide exhibited partial inhibition on RyR2 single channels with an half-inhibitory concentration of ~ 0.2 μM and a maximal inhibitory efficacy of ~ 23%. To explore the impact of a charged residue on ent-verticilide-RyR2 binding, we introduced a terminal carboxylic acid on a single pentyl side chain. The resulting compound lost its inhibitory activity, increased RyR2 single channel open probability, and increased spark frequency in the Ca spark assay. Thus, we named this analog activert. Single-channel analysis revealed that activert reduced mean closed time but did not alter mean open time, indicating that activert destabilizes the closed channel, the mechanism that is opposite of the parent compound *ent*-verticilide. Compared to *ent*-verticilide, activert was an order of magnitude less potent (half-activating concentration ~ 30 μM). Activert binding to RyR2 was also confirmed by [^{3}H]-ryanodine binding assay. Our findings highlight the unique versatility of the COD scaffold, which we have leveraged to discover both RyR2 inhibitors and activators. This bifurcated behavior from a single molecular scaffold stands in contrast to other existing RyR2 modulator scaffolds such as Rycals, which to date have yielded only RyR2 inhibitors. Moreover, these findings also emphasize the value of natural product inspired compounds for developing innovative treatments, particularly for cardiac arrhythmias.

Rebekah Stanton

2025 Postdoc Symposium Abstract

An investigation into how microbial communities are influenced by and change over geologic time in the Transantarctic Mountains, Antarctica.

How does life begin? This question has been asked by many ecologists and earth scientists for as long as we have recorded history. Even in recently disturbed ecosystems, new life often flourishes into a complex system relatively quickly, making it difficult to home in on some of the specifics of community assembly.

Antarctica is known for being one of the most hostile environments on Earth. Yet there is still life that is living there and thriving, it's just very small. Such a small and relatively simple ecosystem provides an ideal proxy for studying how life begins and develops over time.

In the Austral summer of 2017, our team traveled to Ong Valley in the Transantarctic Mountains of Antarctica to collect sediment from moraines left behind by retreating glaciers. While the exact exposure age of these sediments is unknown, they still provide a sequence of deposits with relatively increasing exposure ages, from about 10 Ka to 5 Ma. Previously conducted detrital zircon work found that these moraines are all sourced from the same geologic material, further identifying this area as an ideal proxy for investigating how microbial communities change and transform over geologic time.

The samples were taken to the US, where we extracted and sequenced the 16S DNA. With these sequences, our project aims to compare the microbial community analyses of the moraines as they increase in relative age. We aim to dive deeper into how succession occurs and how communities are built from the ground up.

Chemerin Contributes to Sodium Induced Cardiometabolic Disease and Salt-Sensitive Hypertension in Humans

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Abstract

Salt-sensitivity of blood pressure (SSBP) is characterized by blood pressure (BP) changes in response to dietary sodium and is linked to immune cell infiltration in vascular tissues. Perivascular adipose tissue (PVAT) plays a key role in cellular and physiological processes, with PVAT-derived adipokines implicated in hypertension. However, the role of PVAT-derived adipokines in SSBP in humans remains unexplored. One such adipokine, chemerin, promotes immune cell trafficking and contributes to sodium-induced hypertension in salt-sensitive rodent models. This study aimed to investigate how varying sodium intake influences the expression of chemerin-specific receptors (CMKLR1, GPR1, CCRL2) on human monocytes and how chemerin signaling contributes to changes in BP. We hypothesized that increased sodium intake would upregulate these receptors, leading to increased BP. Using bulk RNA sequencing in isolated human monocytes treated with normal or high sodium, our results demonstrated no expression of GPR1, a decrease in CMKLR1 (6248 ± 3839 vs 3489 ± 2664, P = 0.001), and an increase in CCRL2 (1689 ± 548 vs 2395 ± 726, P = 0.007) expression. We performed a CITE-Seq analysis on PBMCs from hypertensive participants to determine how salt sensitivity affects CMKLR1 and CCRL2 expression. We found that CMKLR1 expression did not differ between salt-sensitive (SS) and salt-resistant (SR) participants (SR: P = 0.561, SS: P = 0.462), however, sodium depletion increased CCRL2 expression in SS participants (P = 0.019) compared to SR participants (P = 0.46). Plasma chemerin levels in hypertensive subjects increased significantly with sodium depletion when compared to base and sodium loading (Base: 26 ± 13 vs SL: 31±10 vs SD: 40 ±13, RM one-way ANOVA P = 0.001). BMI was positively correlated to CMKLR1 expression in monocytes (P = 0.033) and CCRL2 expression in DCs (P = 0.025) when going from sodium loading to depletion. Plasma chemerin was positively correlated to BP during sodium loading (P = 0.017) and depletion

(P =0.036), but not at baseline (P = 0.161). Our findings suggest that chemerin and its receptors may play a role in sodium-induced cardiometabolic disease and SSBP.

Funding:
This study was supported by the National Institutes of Health grants R01 HL144941 (AK) D34HP16299, and T32 5T32DK007569-36 (RM)

Character Count (w/o spaces): 1856/3200

Safety and Outcomes of Ventricular Tachycardia Ablation in Pediatric Arrhythmogenic Right Ventricular Cardiomyopathy

Salah Alahwany

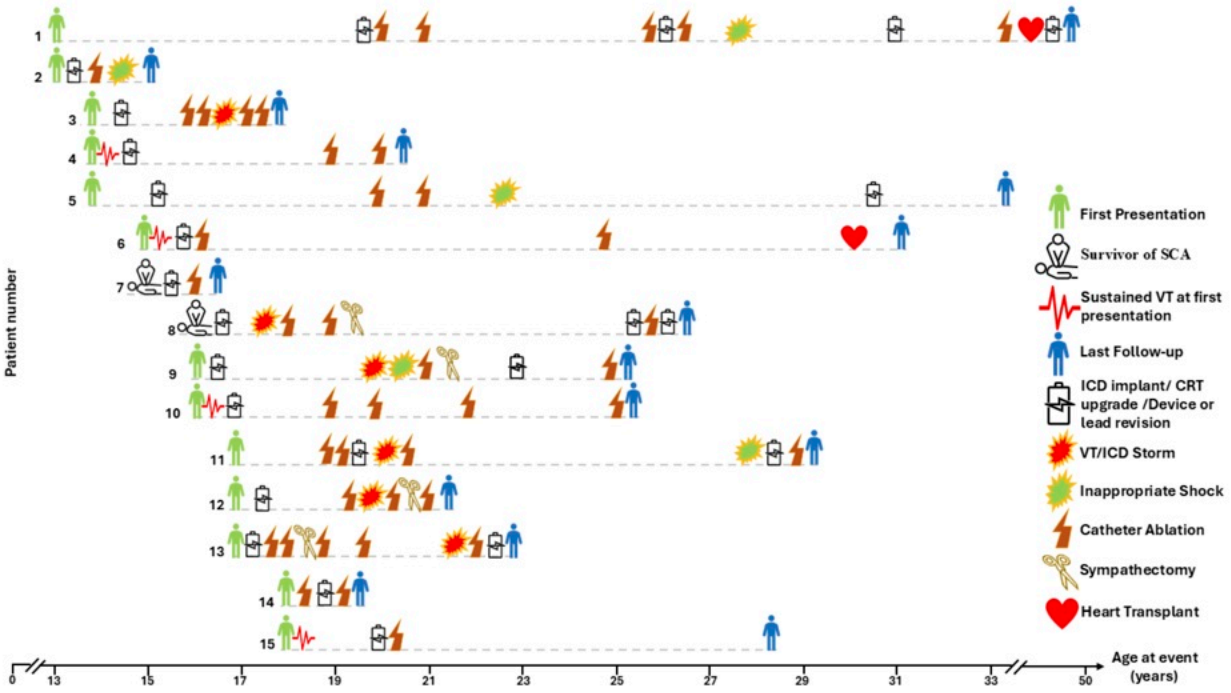
Background: Radiofrequency catheter ablation (RFCA) of ventricular tachycardia (VT) in arrhythmogenic right ventricular cardiomyopathy (ARVC) is safe and reduces ventricular arrhythmia (VA) burden. Previous studies included adult patients and data on pediatric patients is scarce. The objective of our study was to report on the safety and efficacy of RFCA in pediatric ARVC.

Methods: Fifteen patients who fulfilled the 2010 ARVC task force criteria, clinically presented before the age of 18, and underwent VT RFCA procedures at ≤ 21 years old were included. Baseline characteristics, genotypic and phenotypic data, and ablation outcomes were collected.

Results: The mean age at symptom onset was 15.5 ± 1.6 years, and at the index procedure was 18.1 ± 2 years, with 73% of the patients being male. Pathogenic mutation in desmosomal genes was detected in 87%. First presentation symptoms included palpitations (33%), syncope (27%), sustained VT (27%), and sudden cardiac arrest (13%). ECG repolarization abnormalities were present in 93%, and 40% were reported to be athletes. At index RFCA procedure, sustained monomorphic VT was induced in 60%. Electroanatomic mapping showed 100% basal RV epicardial substrate and 54% endocardial low voltage/scar. Repeat VT

ablation was required in 80% over a mean follow-up of 16.4 months. The median number of procedures was 2 (IQR, 2-4), with sustained VT-free survival of 73% over a mean follow-up duration of 21.4 months. No acute periprocedural complications occurred. Bilateral cardiac sympathetic denervation (BCSD) due to recurrent VA was performed in 27%. Eventually, 2 patients (13%) developed advanced heart failure and underwent heart transplantation.

Conclusions: Pediatric ARVC RFCA is safe, but early recurrences are common, requiring repeat ablations and sometimes BCSD. The substrate is mostly epicardial with preserved endocardial voltage. VT free survival is 73% after multiple procedures. Progressive heart failure requiring transplantation occurred in 13% within two decades of initial presentation.


Patient number
1
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27
29
31
33
50
Age at event (years)
First Presentation
Survivor of SCA
Sustained VT at first presentation
Last Follow-up
ICD implant/ CRT upgrade /Device or lead revision
VT/ICD Storm
Inappropriate Shock
Catheter Ablation
Sympathectomy
Heart Transplant

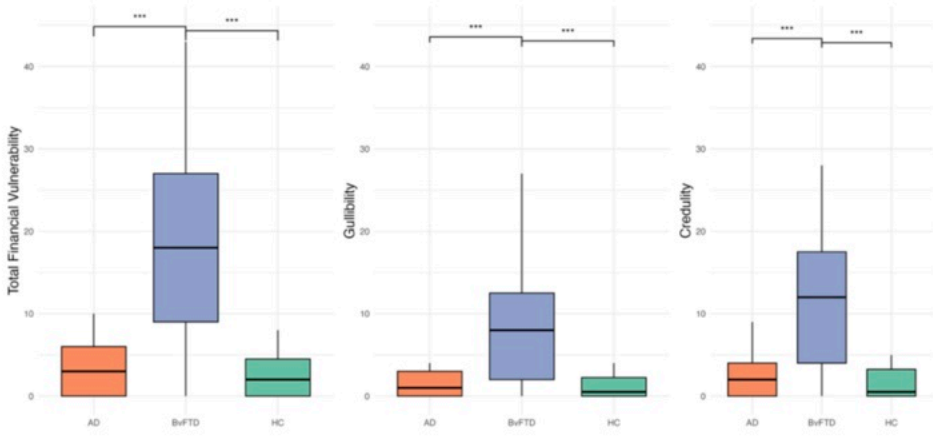
Abstract: *Social cognitive, decision-making, and neuroimaging markers of financial vulnerability in patients with dementia*

Financial exploitation vulnerability (FEV), or the risk of falling victim to financial fraud and scams, is a growing public health crisis in older adults, with $36 billion lost annually to scams. Changes to socioemotional function are hypothesized to contribute to FEV, but how altered social cognition and social decision-making leads to FEV remains unknown. Testing these hypotheses in patients with neurodegenerative disorders is particularly valuable given the increased risk of FEV in patients with dementia and the variance in socioemotional dysfunction across different types of dementia. The objective of the current study is to determine the relationship between FEV and social cognitive and social decision-making dysfunction in patients with dementia.

Informants of 23 patients with Alzheimer's Disease (AD), 50 behavioral variant frontotemporal dementia (bvFTD), and 18 healthy subjects were administered the Social Vulnerability Scale (SVS), a measure of FEV that can be further subdivided into subscales for gullibility and credulity, as well as the Interpersonal Reactivity Index (IRI), a measure for social cognition and perspective-taking. Participants also played two social decision-making tasks in the same visit: the Ultimatum Game, which assesses a participant's willingness to accept fair and unfair offers, and the Trust Game, which assesses a participant's willingness to trust and invest in cooperative and uncooperative partners. Neuroimaging analyses consisted of cortical thickness and atrophy network mapping correlates of behavioral and task measures for all subjects.

Total FEV, gullibility and credulity scores were significantly higher in bvFTD compared to AD patients and cognitively normal controls while controlling for age and sex ($p < 0.001$). Across the entire sample, impaired perspective-taking was associated with higher FEV ($p < 0.001$), higher gullibility ($p = 0.004$), and higher credulity ($p = 0.001$) while controlling for age and sex. In bvFTD patients, greater acceptance of unfair offers in the Ultimatum Game was associated with higher FEV ($p = 0.025$) and higher gullibility ($p = 0.020$). Further, greater investment in the uncooperative partner in the Trust Game was also associated with higher gullibility ($p = 0.036$) in bvFTD. Finally, increased FEV was correlated with atrophy localized to clusters in right lateral orbitofrontal and anterior temporal regions and over-trusting behavior was related to atrophy network mapping changes in the posterior cingulate, precuneus and temporoparietal junction.

Our results suggest that FEV is a more severe problem in bvFTD than AD or controls and is distinctly related to an increased willingness to accept unfairness in social interactions. Changes to how the brain processes social information, identified via neuroimaging and psychometric assessments, may be important tools for identifying patients with dementia that are vulnerable to fraud and scams and for developing interventions to prevent FEV in the future.



Group differences in financial exploitation vulnerability
Financial vulnerability, gullibility and credulity scores in AD, bvFTD and HC groups. (**A**) SVS aggregate total social (financial) vulnerability scores were significantly higher in bvFTD (blue) than AD (orange) and HC (green) in a one-way ANCOVA test while controlling for age and sex. (**B**) SVS gullibility subscale scores were significantly higher in bvFTD than AD and HC, and (**C**) SVS credulity subscale scores were significantly higher in bvFTD than AD and HC.

Alpha cell antigen presentation drives CD8⁺ T cell infiltration in the aging pancreas and is reversed by calorie restriction

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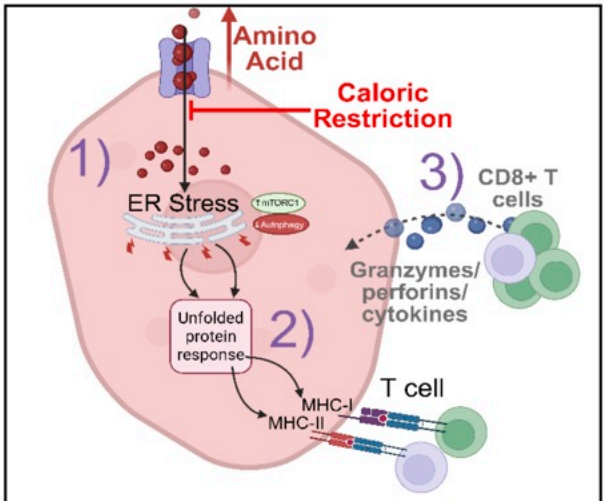
Aging is a major risk factor for type 2 diabetes and cardiovascular diseases. Dietary interventions such as calorie restriction (CR) have been shown to reduce the risk of these age-related diseases by lowering cellular metabolic stress and improving insulin sensitivity. Our research group found that aging independently increases nutrient (amino acid) stress and inflammatory signaling in the human pancreas. Notably, we observed infiltration of activated CD8⁺ T cells in the pancreas, which may contribute to early immune dysregulation and increase the risk of autoimmunity prior to diabetes onset. Unexpectedly, we found that the signals recruiting CD8⁺ T cells originated specifically from the major histocompatibility complex class I (MHC-I) antigens expressed on pancreatic alpha cells; the cells responsible for secreting glucagon, a hormone that counteracts the effects of insulin. This suggests a novel mechanism by which beta cells, responsible for insulin production, may be indirectly harmed by immune responses initiated by neighboring alpha cells. Strikingly, this pattern was recapitulated in aged mice (80 weeks old), but was reversed when the animals were subjected to a 20% CR diet. CR eliminated CD8⁺ T cell infiltration in pancreatic islets and suppressed MHC-I expression in alpha cells. Furthermore, intercellular communication analysis (derived from single cell RNA sequencing) revealed a marked reduction in signaling between antigen-presenting alpha cells and adaptive immune cells (B and T lymphocytes) after CR, suggesting that CR not only improves metabolic health but also reshapes the immune landscape of the aging pancreas. This work highlights the potential for targeting nutrient metabolism to mitigate age-related immune activation and islet inflammation, ultimately enhancing metabolic health across the lifespan.



Proposed model for aging and calorie restriction in endocrine alpha cells. Age-induced nutrient stress from impaired protein folding triggers endoplasmic reticulum stress responses (1), initiating MHC translation and surface antigen presentation (2), and further promoting T cell recruitment and cytotoxic effector function (3).

Zahrat El Oula

Ribosomes are universally conserved RNA-protein complexes that catalyze protein synthesis in all cells. Particularly, the structure of the eukaryotic 40S subunit comprises the head, platform and body, which are composed of 18S rRNA and 33 ribosomal proteins (RPs). Over 200 binding assembly factors (AFs), including proteins, protein complexes and small nucleolar ribonucleoproteins, ensure the production of the small and large ribosomal subunits.

RNAs are well-known to be prone to misfolding, and misfolding of nascent ribosomal RNA (rRNA) has been demonstrated *in vitro*, when chaperones are not present. Moreover, multiple ribosome assembly routes have been identified, especially *in vitro*, which do not all progress to mature ribosomes.

Along the productive ribosomal pathway, structural studies have revealed multiple conformational transitions as the subunit assembles from an early processosome via a late processosome, into intermediate and then late pre-40S intermediates. These transitions are integrated with rRNA processing steps. Thus, the early processosome is blocked prior to the first rRNA cleavage step at so-called site A0, while the next intermediate, the late processosome, is processed at the A0 site, but stalled prior to the next step, cleavage at site A1. Conversion of the early to the late processosome is linked not just to A0 processing, but also to a switch in the UtpB subcomplex (composed of Utp1, Utp21, Utp12, Utp13 and Utp6 and Utp18): by changing the Utp1 and Utp21 interface, their interaction partners Utp12 and Utp13 are rotated to a vastly different location with respect to the rest of UtpB and the processosome. This enables the recruitment of a subset of late-binding processosome factors, which ultimately enable rRNA processing. How this transition is promoted in cells remains entirely unknown.

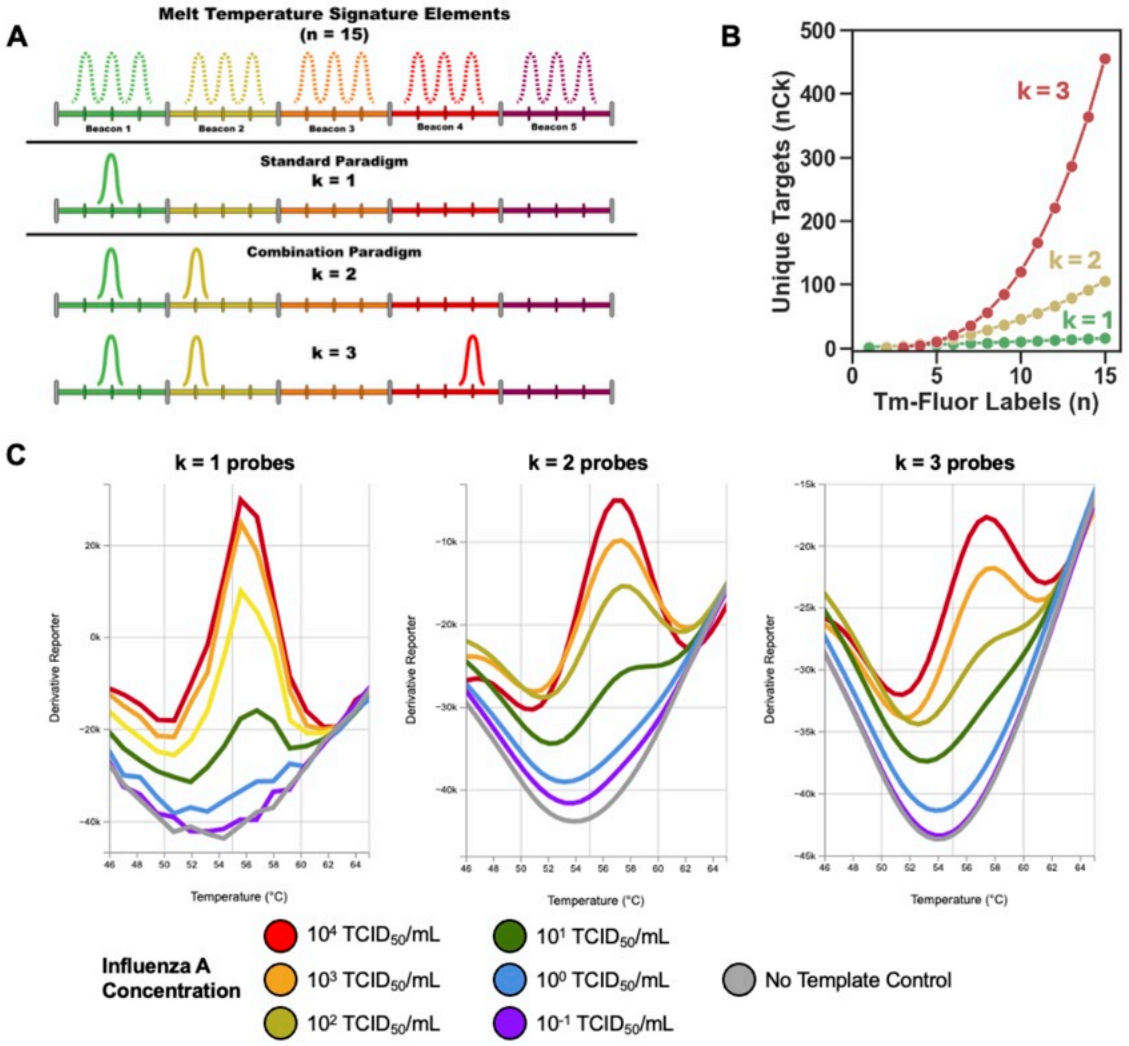
Our data showed that The DEAD-box ATPase Has1 separates Rrp5 and Rrp36, allowing Rrp5 to reposition to the platform, thereby promoting ribosome assembly and enabling rRNA processing. In addition, our biochemical, structural and genetic analyses demonstrate that a subset of late-binding factors fail to assemble in the presence of inactive Has1, while the remaining ones fail to reposition. Moreover, destabilizing the late processosome produces synthetic genetic interactions, while destabilizing the early processosome partially rescues the inactivation of Has1. Thus, these data show that Has1 activity can be partially substituted by promoting the UtpB switch.
Because the interactions of Rrp5 at the platform stabilize the UtpB switch, the Has1-mediated repositioning of Rrp5 enables the UtpB switch, allowing for the recruitment of late-binding processosome factors, and thereby the activation of rRNA processing.

Postdoc Fair Abstract Submission

Highly scalable, combinatoric PCR strategy enables augmented panel-based multiplexing for single target detection

Introduction

Polymerase chain reaction (PCR) is one of the most widely used diagnostic technologies due to its unparalleled sensitivity and specificity. Multiplex PCR enables simultaneous detection of multiple target sequences, broadening the diagnostic scope and conserving time and resources. Each additional PCR that can be added to a reaction increases the utility. However, assuming one could combine as may individual PCR reactions as desired into a single tube, state-of-the-art PCR instruments and detection reagents limit the maximum number of PCR reactions to one reaction for each of the instrument's fluorescence channels. To overcome these limitations, approaches for combining fluorescence color and sequence melting temperature (Tm) were previously explored. The strategy is limited by following the standard paradigm of one label (Tm-fluorescence) per one target analyte, and, therefore, restricts the number of uniquely discernable targets within a given design space to the number of unique Tm-fluorescence labels. In this work, we aim to counter this paradigm by increasing the number of uniquely identifiable targets within a given design space through label combinatorics. By selectively increasing the number of Tm-fluorescence labels for a given target, the multiple labels provide a combined, unique target-specific signature (**Figure 1A**). This reimagined signature output strategy, achievable through relatively simple experimental modifications, significantly increases the number of target analytes within a given design space (**Figure 1B**). This paradigm shift reduces design burden and reagent cost. Further, it improves the practicality of the platform genetic technology – requiring less Tm-fluorescence signals within a design space to reach high order multiplexability. The Tm-fluorescence signals are generated by modified PCR hydrolysis probes, called "mediator probes" consisting of a 5'-flap sequence designed to be cleaved by the exonuclease activity of polymerase during amplification. Following cleavage, the 5'-flap hybridizes to a molecular beacon reporter to produce a unique Tm-fluorescence output. To generate multiple output labels, multiple mediator probes are designed for the same hybridization site on the target in competition. Here, we study how the competition-based labeling strategy impacts the analytical performance of the assay. Competitive probes were designed to produce up to three unique labels in a single reaction for the detection of Influenza A. Analytical sensitivity and specificity were observed as the number of competitive probes increased from one to three across titered concentrations of spin-column extracted Influenza A (BEI Resources, NR-15241). By increasing the number of combined labels (k) for a single target, the number of unique targets increases from equal to the number of targets in a design space (n) to n choose k (nCk), which can be expressed as $nCk = n!/k!\,(n-k)!$. With a given design space of n = 15 Tm-fluorescence possible signals, the standard paradigm of one signal per target has a maximum number of uniquely identifiable targets of 15. Increasing combined signals to k = 2 and k = 3 results in a maximum of 105 and 455 unique identifiers for a single target, respectively (**Figure 1B**). Signals are increased by introducing mediator probes with varied 5'-flap sequences in combination. For a single probe (k = 1), the combination PCR assay resulted in melt analysis-based detection for 6 of 6 extracted influenza A samples at 10^1 $TCID_{50}$/mL and 3 of 6 samples at 10^0 $TCID_{50}$/mL. When an additional competitive probe was introduced (k = 2), influenza A at 10^1 $TCID_{50}$/mL was detected 6 of 6 times and 10^0 $TCID_{50}$/mL was detected in 1 of 6 replicates. For k = 3, 6 of 6 replicates, 2 of 6 replicates, and 0 of 6 replicates were detected for 10^2 $TCID_{50}$/mL, 10^1 $TCID_{50}$/mL, and 10^0 $TCID_{50}$/mL, respectively. Across all combinatoric studies, assay specificity was maintained with no false positives. Representative melt curves for one of the signals across number of mediator probes and titered influenza A concentration is demonstrated in **Figure 1C**. These data suggest that the combinatoric PCR design can achieve a significant increase in uniquely discernable targets, however, the required increase in mediator probe negatively impacts the assay analytical sensitivity. While the current status of the assay results in a trade-off between scalability and sensitivity, the sensitivity of the assay remains high due to the unparalleled sensitivity of PCR as a diagnostic method. Future work will focus on testing additional combinatoric schemes and their respective impact on assay performance. Additionally, the scalability of the assay will be demonstrated with a proof-of-concept highly multiplexed diagnostic for respiratory infections.


A
Melt Temperature Signature Elements
(n = 15)
Beacon 1
Beacon 2
Beacon 3
Beacon 4
Beacon 5
Standard Paradigm
k = 1
Combination Paradigm
k = 2
k = 3
B
Unique Targets (nCk)
Tm-Fluor Labels (n)
k = 3
k = 2
k = 1
C
k = 1 probes
k = 2 probes
k = 3 probes
Derivative Reporter
Temperature (°C)
Influenza A Concentration
10⁴ TCID50/mL
10³ TCID50/mL
10² TCID50/mL
10¹ TCID50/mL
10⁰ TCID50/mL
10⁻¹ TCID50/mL
No Template Control

Carlos Tellet Cabiya

Assessing Cibenzoline as an Alternative for Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, inherited arrhythmogenic disorder triggered adrenergic stimulation in structurally normal hearts, often linked to CASQ2 mutations and affecting young individuals. While beta-blockers are the cornerstone treatment, their limited efficacy necessitates alternative therapies such as flecainide or implantable defibrillators, which may be consider by patient specific factors. Cibenzoline, a multi-class antiarrhythmic agent with sodium and potassium channel inhibition and modest Calcium channel effect, has emerged as an alternative therapeutic candidate for CPVT. This study aims to investigate cibenzoline mechanism and therapeutic efficacy in CASQ2 related CPVT, comparing its effect to flecainide. We present a pediatric case with a homozygous CASQ2 variant (c.939+5G>C) and conduct in vitro RyR2 single channel recordings, and SR Ca handling assays in permeabilized cardiomyocyte. In vivo, we evaluate cibenzoline antiarrhythmic effects using catecholamine challenge in Casq2-/- mouse CPVT model and and a triple crossover study to compare cibenzoline vs flecainide vs vehicle. Cibenzoline significantly reduced dysrhythmic episodes in both the patient and the mouse models with results (P=0.0023 for arrhythmia burden; P=0.020 for arrhythmia score), despite less RyR2 inhibition than flecainide and minimal Ca^{2+} handling suppression. These results suggest that cibenzoline operates via a mechanism that is distinct from flecainide's action on RyR2 channels. These findings underscore the importance of developing RyR2 targeted therapies with precise mechanistic specificity, which may unlock more effective and individualized treatments for CPVT. Further research is warranted to elucidate CPVT pathophysiology and highlight new avenues for therapeutic innovation.

The Role of GPNMB in Infection-Mediated Endothelial Dysfunction

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Sepsis, a life-threatening condition caused by a dysregulated immune response to infection, remains a leading cause of death worldwide. A key feature of sepsis is vascular dysfunction, marked by endothelial cell (EC) activation, disrupted vascular tone, and microvascular leakage—all of which greatly contribute to organ failure. Despite extensive research, effective treatments targeting endothelial dysfunction in sepsis continue to be lacking. Nonmetastatic melanoma glycoprotein B (GPNMB), a transmembrane glycoprotein found on endothelial and immune cells, has been linked to the regulation of inflammation, metabolism, and tissue repair. However, its role in sepsis-induced vascular dysfunction is not well understood. To explore the role of GPNMB in endothelial inflammation during infection, we conducted experiments using human microvascular endothelial cells (HMVECs) with GPNMB knockdown (siGPNMB) and exposed them to heat-killed *Escherichia coli* (HKEC), a common sepsis pathogen. Additionally, we utilized a polymicrobial sepsis model (Enriched Cecal Suspension) to induce sepsis in DBA/2J (KO) and DBA/2J-Gpnmb+ (WT) mice. Under basal conditions, siGPNMB cells exhibited increased transendothelial electrical resistance, indicating changes in pathways related to barrier function. However, upon HKEC exposure, siGPNMB cells showed greater barrier dysfunction compared to controls. Furthermore, siGPNMB cells displayed impaired viability, proliferation, and migration after HKEC exposure. Metabolic assessments revealed that HKEC exposure decreased oxygen consumption and increased extracellular acidification in control cells, but these metabolic shifts were absent in siGPNMB cells, suggesting a critical role for GPNMB in metabolic reprogramming during infection. In vivo, six hours after sepsis induction, both WT and KO Sepsis mice exhibited reduced blood pressure compared to SHAM mice, with KO mice showing a more pronounced reduction. Although the mice's blood pressure returned to normal within 72 hours, we observed changes in vascular reactivity. Phenylephrine-induced contraction was significantly reduced in septic animals, with KO mice exhibiting greater impairment. And endothelium-dependent relaxation in response to acetylcholine was enhanced in septic KO mice, indicating dysregulated vascular tone. Also, cytokine analysis at 72 hours revealed elevated pro-inflammatory cytokine levels in SHAM KO mice compared to SHAM WT mice (TNFα, IL-6 and IFNγ). Following sepsis induction, cytokine levels increased significantly in both groups, with KO mice showing a more intense inflammatory response. These results suggest that GPNMB deficiency exacerbates vascular inflammation and disrupts immune homeostasis during sepsis. In summary, our study highlights the crucial role of GPNMB in maintaining vascular stability during infection. The absence of GPNMB impairs endothelial barrier integrity, metabolic reprogramming, and vascular reactivity, while amplifying inflammatory responses in a polymicrobial sepsis model. These findings provide valuable insights into the mechanisms underlying sepsis-induced vascular dysfunction and identify GPNMB as a potential therapeutic target for mitigating endothelial damage in sepsis.

A Systematic Umbrella Review of Firearm-Related Harms Prevention Research

Colleen Walsh

Abstract

Firearm-related harm is a critical public health issue with fragmented evidence across disciplines. This umbrella review synthesized existing review-level literature to map the evidence base and guide prevention efforts. The review aimed to characterize existing firearm-related reviews, assess methodological rigor, and identify evidence gaps relevant to public health and violence prevention. A systematic search of ProQuest (including Social Science and PsycINFO), Medline, and Web of Science was conducted through August 2024 following PRISMA guidelines. Peer-reviewed systematic, scoping, and meta-analytic reviews published in English on firearm-related topics were included. From 5,662 records screened using Covidence, 83 reviews were selected after full-text screening. Data extraction used an iteratively refined codebook capturing descriptive, methodological, and content variables, with thematic synthesis organizing findings. The included reviews addressed diverse topics such as suicide prevention, interpersonal violence, unintentional injury, firearm ownership, and policy impacts. Suicide and firearm policy were most frequently examined. Quality varied, with few reporting pre-registration or funding sources. Meta-analyses were less common than narrative reviews. Intervention evaluations were limited and often lacked rigorous designs. Youth-specific firearm outcomes were underrepresented, and cross-sector approaches were rare. Methodological inconsistencies and heterogeneous outcome measures hindered comparability across studies. Despite growth, the firearm review literature remains uneven, limiting evidence-based policymaking and intervention development. Strengthening methodological rigor, including transparency and preregistration, and prioritizing evaluation of interventions, especially for youth and multi-sector collaboration, are critical. Applying prevention science frameworks can unify findings, enhance early intervention, and inform comprehensive strategies. Cross-sector

coordination grounded in these principles is essential to reduce firearm-related harm, promote equity, and improve community safety. Future research should emphasize rigorous designs, broaden populations studied, and integrate multisystem approaches to advance public health impact.

Keywords: umbrella review, firearms, guns, prevention science

Human kidney organoids exhibit an intrinsic capacity to biosynthesize cholesterol and estrogen

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Background

The kidney plays a central role in blood pressure and sodium homeostasis. Renal estrogenic signaling enhances sodium excretion and lowers blood pressure. While estrogen biosynthesis has been demonstrated in rodent kidneys, the endogenous capacity in the human kidney remains unclear. Given that cholesterol is a key precursor for estrogen synthesis, we hypothesized that human kidney organoids derived from induced pluripotent stem cells (iPSC) possess intrinsic cholesterol biosynthetic capacity to support local estrogen production.

Methods

We analyzed publicly available RNA-seq datasets from day 26 human kidney organoids for key cholesterol biosynthesis genes and identified transcripts for 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), the rate-limiting enzyme in cholesterol biosynthesis and its

upstream transcriptional regulator SREBP2. To validate these findings, we differentiated kidney organoids from iPSC on transwells using the Takasato protocol *in vitro.* We collected culture media at days 10, 12, 15 (n=4 per time point, pooled from two independent batches). We performed immunofluorescence at days 17 and 19 to localize expression of HMGCR, CYP11A1, which catalyzes the conversion of cholesterol to pregnenolone, and aromatase (CYP19A1), which catalyzes the rate limiting step in estrogen biosynthesis. We quantified cholesterol and 17-β estradiol levels in culture media using the Amplex Red assay and ELISA, respectively.

Results

In-silico analyses revealed expression of HMGR and SREBP2 in day 26 organoids. We confirmed HMGCR co-localization with the LTL-positive proximal tubule-like structures, while CYP11A1 and CYP19A1 localized to ECADHERIN-positive tubular regions. We validated HMGCR protein expression by Western blot, corroborating the transcriptomic and immunofluorescence data. Biochemical analysis showed increases in total cholesterol (day 12 vs 10, p=0.04), free cholesterol (day 15 vs 10, p = 0.03) and 17-β estradiol (day 15 vs control media, p=0.04).

Conclusion

We demonstrate that human iPSC-derived kidney organoids have functional cholesterol biosynthesis and temporally regulated estrogen production, supporting a model in which locally synthesized cholesterol may contribute to local estrogenesis. Further investigations are needed to elucidate the role of renal steroidogenesis in regulating natriuresis and blood pressure.

Key words:

Cholesterol, estrogen, kidney organoids, sodium transport (Na), hypertension

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