From Gaps to Gateways: Advancing Research on Chronic Conditions in Women

Poster Abstract Book

10th Anniversary Vivian W. Pinn Symposium

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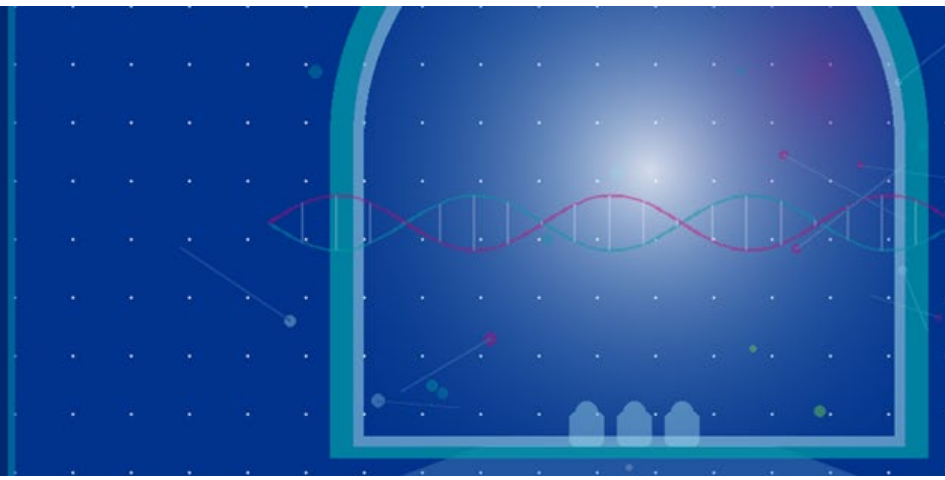
Contents



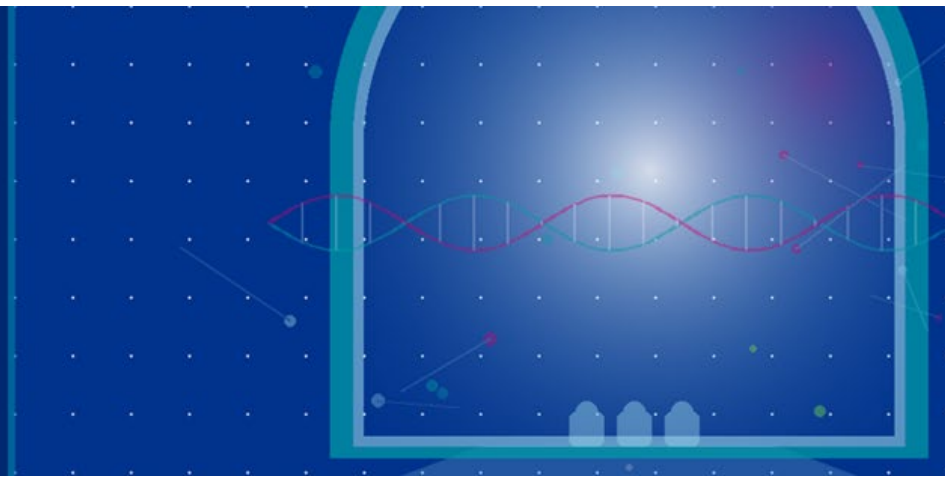
NIH Intramural Program Abstracts

A Cytoskeletal Master Switch That Orchestrates Pathologic Vascular Remodeling in Pulmonary Arterial Hypertension (PAH)

Keytam Awad, Staff Scientist, Clinical Center
Mentor: Robert Danner
Authors: Keytam S. Awad;* Shuibang Wang; Daniels Konja; Gabriela A. Ferreyra; Christina Zhu; Jason M. Elinoff; Robert L. Danner

Background: Loss-of-function mutations in bone morphogenic protein receptor type 2 (BMPR2) disrupts cytoskeletal organization in PAH, a female predominant disease. While actin polymerization is known to underlie disruption of cytoskeletal architecture, the role of α-tubulin, another key cytoskeletal regulator subject to diverse post-translational modifications, has not been investigated in this context. Vasohibin 1 (VASH1), the elusive tubulin carboxypeptidase that mediates α-tubulin detyrosination, is reduced in BMPR2 deficient human pulmonary artery endothelial cells (HPAECs). We propose that imbalances in α-tubulin detyrosination/tyrosination disrupts endothelial homeostasis and contributes to PAH pathogenesis, and that targeting this pathway may offer a therapeutic strategy.
Methods/Results: In BMPR2-silenced HPAECs, both VASH1 expression and detyrosinated α-tubulin levels were markedly decreased. Similar to BMPR2 knockdown, silencing VASH1 decreased detyrosinated α-tubulin and triggered a PAH-like proliferative, pro-migratory, and anti-apoptotic phenotype. Notably, co-silencing BMPR2 and TTL, a tubulin tyrosine ligase that adds tyrosine to the COOH terminus of α-tubulin, increased α-tubulin detyrosination. BMPR2 and/or TTL silencing resulted in 1180 differentially expressed genes (FDR <0.01), and more than half (n=604) were regulated in opposite directions by BMPR2 or TTL loss. These genes include components of focal adhesion kinase (FAK) and Rho GTPase signaling pathways, representing a subset of the BMPR2 deficiency-associated transcriptome responsive to the detyrosination state of the endothelial cytoskeleton. Importantly, very low concentrations of TPI-287, a microtubule-stabilizing agent under clinical investigation for non-PAH diseases, dose-dependently increased detyrosinated α-tubulin, thereby suppressing proliferation and migration, and restoring VE-cadherin expression at the plasma membrane of BMPR2-deficient HPAECs. **Conclusion:** Increasing α-tubulin detyrosination, either by silencing TTL or through the use of small molecule inhibitors, represents a novel and previously unexplored strategy for correcting cytoskeletal dysregulation and pathologic vascular remodeling in PAH.

Keywords: Cytoskeleton, Endothelial Homeostasis, A-tubulin Detyrosination

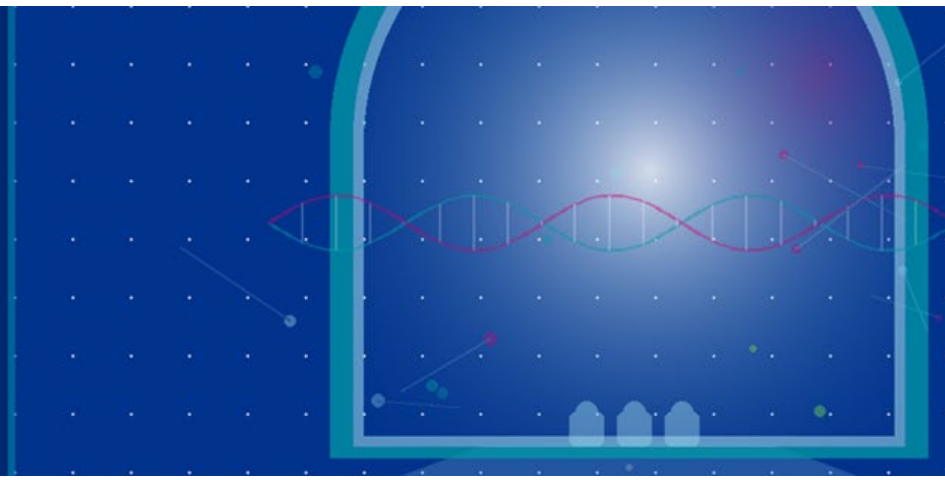


A DNAJA3 Regulatory Variant and Sex-Aware Risk Stratification for NASH-Related Hepatocellular CarcinomaX

Yuto Shiode, Visiting Fellow, National Cancer Institute
Mentor: Xin Wei Wang
Authors: Yuto Shiode;* Ching-wen Chang; Xin Wei Wang

Scientific background: Chronic metabolic liver disease, including NAFLD/NASH, is a major driver of hepatocellular carcinoma (HCC). Because metabolic risk profiles and clinical recognition can differ across sexes and life stages, risk stratification approaches that are robust in women are needed.
Research question: We asked whether common regulatory variants contribute to NASH-associated HCC risk by altering mitochondrial stress-response pathways. We hypothesized that a regulatory variant controlling DNAJA3 expression promotes progression from NASH to HCC.
Experimental design: We screened variants associated with body fat distribution (n=344,369) and tested associations with NASH and HCC in an independent NCI–UMD cohort (n=1,009). We performed eQTL analyses, evaluated long-range regulation using 3D chromatin architecture, integrated ChIP-seq evidence for transcription factor binding, and conducted functional assays including RBFOX2 knockdown and allele-specific luciferase reporter testing.
Results: We identified rs3747579 (TT) as associated with NASH-related HCC and as an eQTL linked to reduced DNAJA3 expression. Lower DNAJA3 expression in HCC correlated with worse prognosis. Although rs3747579 is distal to the DNAJA3 promoter, 3D chromatin data supported allele-specific enhancer–promoter interactions. The rs3747579 locus overlapped a putative RBFOX2 binding site; RBFOX2 knockdown reduced DNAJA3 mRNA levels. In luciferase assays, the rs3747579-CC allele showed higher regulatory activity than TT, supporting allele-specific transcriptional regulation.
Conclusions and implications: These data nominate rs3747579 as a functional regulatory variant influencing DNAJA3 expression and potentially shaping the transition from chronic metabolic liver disease to HCC. The work supports development of genetic and blood-based strategies for identifying high-risk individuals, including women with chronic metabolic conditions, to enable earlier surveillance and prevention.

Keywords: DNAJA3; MASH; Genetic risk stratification

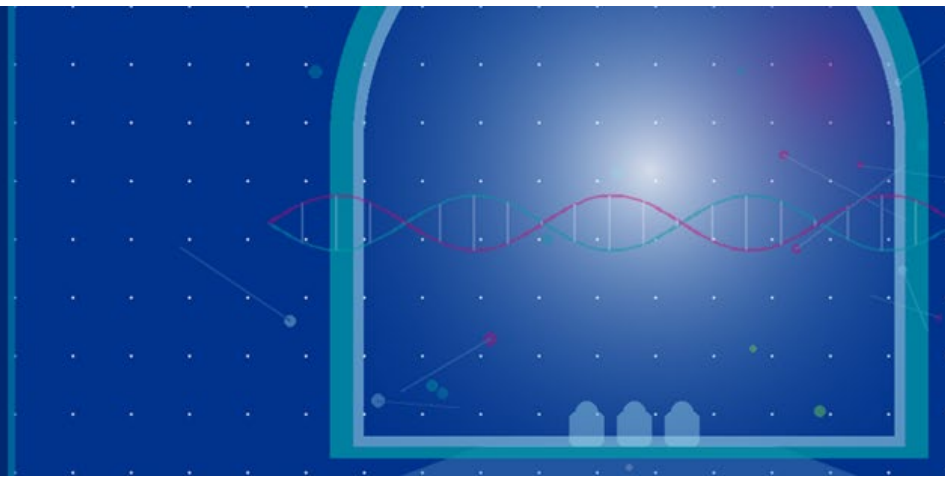


AAV- M3R-DREADD Gene Therapy - a Novel Approach to Pharmacologically Address Xerostomia in Sjögren Disease

Ioana Ghita, Clinical Fellow, National Institute of Dental and Craniofacial Research
Mentor: John Chiorini
Authors: Ioana Ghita;* Sandra Afione; Giovanni Dipasquale; Changyu Zheng; Jay Chiorini

Abstract: Sjögren's disease is a chronic systemic autoimmune disorder affecting ~ 4 million individuals in the U.S., with an estimated 2.5 million cases remaining undiagnosed. The disease predominantly affects women over 40 y/o (female-to-male ratio = 9:1). Its hallmark clinical manifestations are sicca symptoms, characterized by ocular (xerophthalmia) and oral (xerostomia) dryness due to damage of the lacrimal and salivary glands. Current therapeutic options rely mainly on muscarinic agonists such as pilocarpine and cevimeline, which provide limited benefit and are frequently associated with systemic cholinergic adverse effects, including sweating, urinary frequency, bronchoconstriction, cardiovascular instability, fluid retention etc. Designer receptors exclusively activated by designer drugs (DREADDs) offer a novel, targeted approach for stimulating salivary secretion. The hM3R-DREADD, the modified M3 muscarinic receptor, responds to synthetic ligands (e.g., clozapine-N-oxide, compound 21, perlapine), but not to acetylcholine, enabling selective salivary stimulation while avoiding off-target side effects. We hypothesize that AAV-mediated delivery of hM3R-DREADD to salivary gland acinar cells will enhance fluid secretion by promoting aquaporin (AQP) translocation to the apical membrane through physiologic M3R signaling pathways. Results: In vitro stimulation of AAV2-hM3R-DREADD–transduced HEK293T cells induced robust intracellular calcium mobilization with perlapine (10 μM), producing the strongest response (49.4% of ionomycin maximum). In vivo, perlapine (10 mg/kg, IP) increased salivary flow in parotid and submandibular glands of C57BL/6 mice transduced with AAV44.9-hM3R-DREADD, with peak secretion observed at 4-8 weeks post-cannulation and consistently greater responses in submandibular glands. Therapeutic efficacy was confirmed in Sjögren's (AAV2-LAMP3) and radiation-induced xerostomia mice models, where salivary output correlated directly with vector dose. Notably, AQP5 knockout mice exhibited no salivary response following DREADD activation, indicating that AAV-hM3R-DREADD construct operates via the same signaling cascade as the endogenous M3R, requiring the presence of AQP5 to function. Conclusion: hM3R-DREADD gene therapy enables controllable, potent salivary stimulation via physiologic M3R signaling while avoiding the adverse effects of conventional muscarinic agonists, representing a promising novel treatment for xerostomia in Sjögren's disease.

Keywords: Sjögren's Disease, Xerostomia, M3R-DREADD

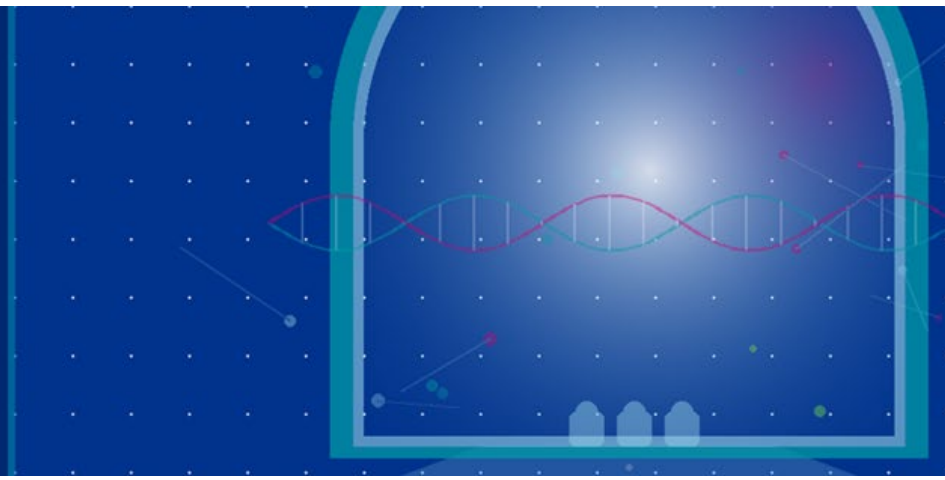


Amygdala Choreographs Pain in Times of Stress

Nisa Roy, Visiting Fellow, National Center for Complementary and Integrative Health
Mentor: Yarimar Carrasquillo
Authors: Nisa Roy;* Sudhuman Singh; Jordan Becker; Jonathan Garcia; Se Rin Lee; Daviana Menendez Escalera; Maxime Thouaye; and Yarimar Carrasquillo

Abstract: Pain responses differ by sex, with women reporting more frequent pain while also exhibiting greater pain inhibition capabilities. Enhanced pain tolerance is observed in women following stress manipulation. Delineating the anatomical and physiological factors underlying pain response is essential for understanding the impact of stress on women. We aim to dissect how stress-induced changes in forebrain limbic structure, the central amygdala (CeA) cells, and circuits contribute to stress-induced changes in pain processing. CeA, comprising of heterogenous group of neurons, includes somatostatin-expressing cells (CeA-Som) that once activated drives analgesia. At the circuit level, CeA is well affiliated with periaqueductal gray (PAG). In this study, we hypothesized that stress increases excitability in CeA-Som and PAG-projecting CeA neurons, enhancing inhibitory synaptic inputs into GABAergic PAG neurons, leading to stress-induced analgesia (SIA). Combining forced swim with the formalin test model of inflammatory pain in the mouse model, we validated SIA by observing delayed and reduced formalin-induced nociceptive behaviors post-forced swim. Ongoing experiments evaluate the co-expression of the neuronal activity marker cFos with various CeA markers to determine activated CeA neurons during SIA. Pilot chemogenetic experiments show that activation of CeA-Som neurons reduces formalin-induced spontaneous behavior in males but not in females, whereas inhibition of CeA-Som and CeA-PKCδ cells resulted in partial reversal and amplification of SIA, respectively, suggesting that these CeA neurons contribute to SIA. Optogenetic-assisted circuit mapping confirmed CeA neurons project to PAG. Using whole-cell patch-clamp electrophysiology in acute mouse brain slices, we confirmed functional channelrhodopsin (ChR2) expression by recording optically evoked currents and action potential firing in transduced CeA neurons. Notably, we demonstrated that the inputs from the CeA to the PAG are monosynaptic. Pilot experiments involving bilateral chemogenetic inhibition of PAG-projecting CeA neurons resulted in partial reversal of SIA. These results will advance our understanding of how pain responses are altered in women.

Keywords: Pain, Stress, Amygdala

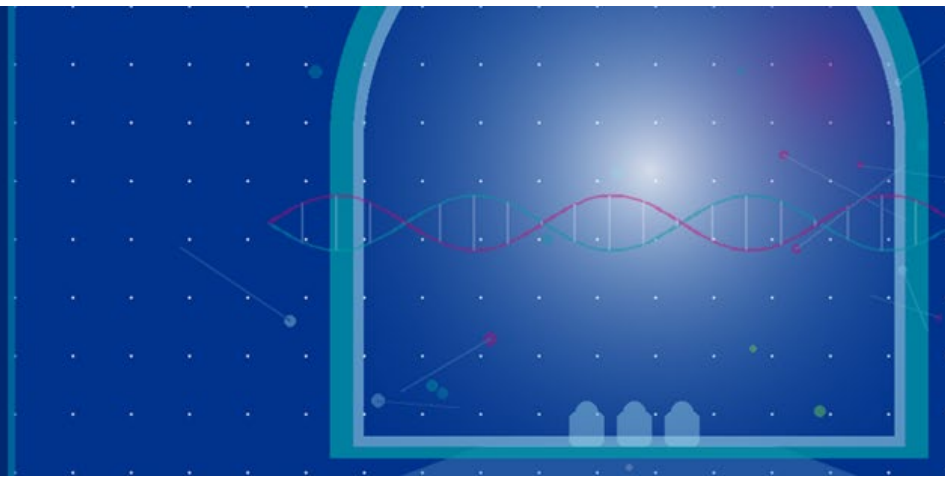


Beta-Arrestin-2/ERK-1/2 signaling is essential for melanocortin 4 receptor-mediated suppression of food intake

Misbah Rashid, Visiting Fellow, National Institute of Diabetes and Digestive and Kidney Diseases
Mentor: Jurgen Wess
Authors: Misbah Rashid,* Lei Wang, Oksana Gavrilova, Zhenzhong Cui, Jürgen Wess

Introduction & objectives: Obesity is the leading cause of type 2 diabetes (T2D), driving metabolic dysfunction through complex neuroendocrine and signaling pathways. The melanocortin-4 receptor (MC4R), a critical regulator of energy balance and glucose homeostasis, has emerged as a key therapeutic target for obesity and associated metabolic disorders. The MC4R is coupled to Gs and other heterotrimeric G proteins but can also engage beta-arrestin 2 (barr2), a cytoplasmic protein that modulates receptor signaling and trafficking and can also act as signaling protein in its own right. Interestingly, specific MC4R variants with enhanced barr2 recruitment confer up to a 50% lower risk of developing obesity, T2D, and related metabolic disorders. However, the molecular mechanisms by which barr2 regulates MC4R-dependent metabolic outcomes remain unexplored. For this reason, we investigated the potential role of barr2 in regulating MC4R-mediated metabolic effects and the underlying molecular mechanisms.
Methods: We generated and analyzed mice that lacked barr2 specifically in MC4R-expressing neurons (MC4R-barr2-KO mice) using Cre-Lox P strategy. Mutant mice and littermate controls were analyzed for subsequent metabolic analyses.
Results: Compared to control littermates, the MC4R-barr2-KO mice showed enhanced food intake, increased adiposity, glucose intolerance, and insulin resistance. To more directly investigate the role of barr2 in MC4R-mediated signaling, we injected MC4R-barr2-KO mice and control littermates with melanotan II (MTII), a potent MC4R agonist. While MTII reduced food intake in control mice, this effect was greatly reduced in MC4R-barr2-KO mice. Similarly, the FDA-approved MC4R agonist setmelanotide did not suppress food intake in the absence of barr2 suggesting that impaired barr2 function may limit therapeutic efficacy in obesity. Interestingly, selective re-expression of barr2 in the paraventricular nucleus of MC4R-barr2-KO mice restored control-like MTII effects.
Conclusion: These data highlight the key role of barr2 in mediating the beneficial metabolic effects of MC4R signaling on energy and glucose homeostasis. MC4R agonists capable of recruiting barr2 with high efficacy may prove therapeutically useful as novel anti-obesity drugs.

Keywords: MC4R, Beta Arrestin, Food Intake, Obesity



Beyond Birth: Properties and Function of Pre- and Postnatal B Cells?

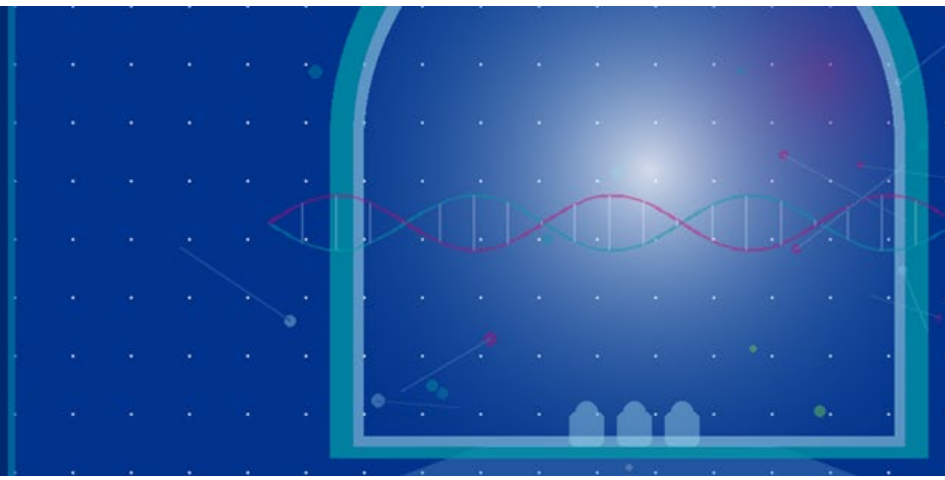
Anastasia De Poulpiquet Du Halgouet, Visiting Fellow, National Institute of Dental and Craniofacial Research

Mentor: Roxane Tussiwand

Authors: Anastasia Du Halgouet,* Fabian Klein, Erfan Jabari, Sebastian Wellford, Anjali Chandroth, Grozdan Cvijetic, Haiting Wang, Siqi Zhao, Harrison Wang, Joanne Shi, Pam Schwartzberg, Mike Kelly, Charlie Seibert, Daniel Martin, Roxane Tussiwand*

Abstract: To date, the functional relevance and properties of prenatal lymphocytes remain elusive. Therefore, we developed a fate-mapping mouse line based on the postnatal expression of the terminal deoxynucleotidyl transferase enzyme (Dntt), that inserts random nucleotides at VDJ-junctions. In our model, we can detect prenatal B cells in any tissue at any age and following any perturbation. We first observed persistence of prenatal cells not only within B1 cells but also across all subsets including marginal zone and follicular B cells. Initial, BCR heavy-chain usage indicated that B cells clustered based on their ontogeny rather than their subset identity. We hypothesize that prenatal B cells are selected on endogenous/maternal antigens, and may be enriched in self-reactive clones, while postnatal B cells likely result from selection on exogenous antigens, including microbiome. Protein microarray results confirmed higher binding to self-antigen for prenatal-derived antibodies. In contrast, broad antibiotic treatment reduced both the number and frequency of postnatal B cells, supporting a partial reliance on microbial-derived antigens. Furthermore, prenatal B cells exhibited intrinsic transcriptional differences as established by scRNAseq. Interestingly, unsupervised clustering revealed a distinct cluster of prenatal cells comprising of various B cell subsets. Moreover, we established a significant difference in the responsiveness to stimulations between pre- and postnatal B cells, i.e. T-cell dependent, TLR-mediated, and BCR-crosslinking. Notably, prenatal B cells exhibited a significantly lower proliferation following TLR or T-cell dependent activation but were refractory to anti-IgM-induced apoptosis, suggesting a certain degree of anergy in this compartment, that would explain the enrichment in self-reactive clones. Given the persistence of an anergic prenatal pool of B cells, capable of recognizing self, we hypothesized that this subset could be regulatory by inhibiting the postnatal pool. Co-culturing of pre- and postnatal B cells revealed reduced activation of postnatal cells as measured by decreased CD69 expression, supporting a suppressive effect by prenatal B cells. This suppression appeared to be contact-independent, suggesting that they release inhibitory cytokines. Collectively we envision that upon tissue damage under inflammatory or infection conditions, prenatal B cell activation acts as a break to ensure an appropriate immune response.

Keywords: B Cells, Autoimmunity, Ontogeny

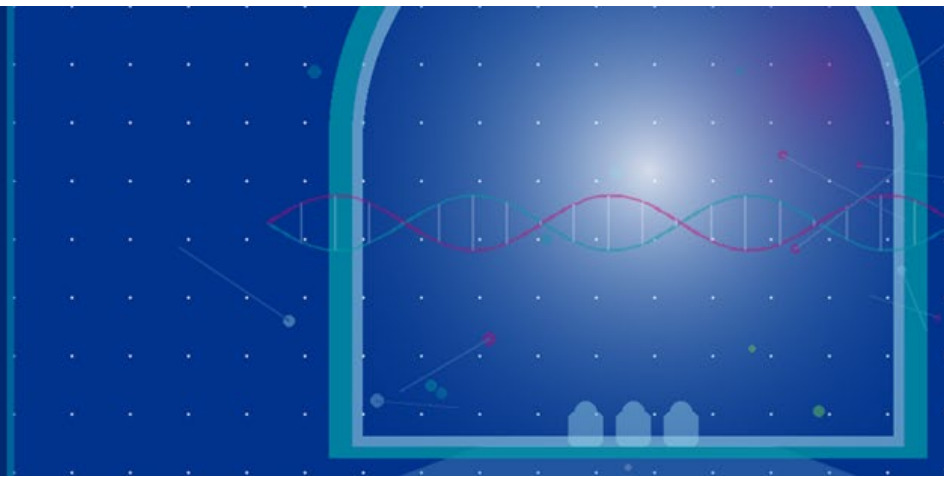


CD44 Knockdown Attenuates the Abnormal Cellular Phenotype of BMPR2-Deficient Primary Human Pulmonary Artery Endothelial Cells

Mohammad Abdul Hai Siddique, IRTA Postdoc, National Heart, Lung, and Blood Institute
Mentor: Jason Elinoff
Authors: Mohammad Siddique;* Li Yuan Chen; Kadija Hersi; Phil Hwang; Zuxi Yu; Keytam Awad; Shuibang Wang; Robert Danner; Jason Elinoff

Background: BMPR2 gene silencing in primary human pulmonary artery endothelial cells (PAECs) produces a proliferative, hypermigratory PAH-like cellular phenotype. Genome-wide expression profiling in BMPR2-silenced cells uncovered CD44, a cancer stem cell marker associated with tumor progression and metastasis, among the top upregulated transcripts. Therapeutic strategies that block CD44 or reduce its expression are currently in various stages of development for cancer. Thus, mechanistic studies investigating the contribution of CD44 to vascular remodeling in PAH may reveal new therapeutic targets. Hypothesis: Upregulation of CD44 contributes to the abnormal phenotype of BMPR2-deficient PAECs and thus may contribute to vascular remodeling in PAH.
Aims: Determine the effect of CD44-silencing on gene expression and cell proliferation in BMPR2-deficient PAECs.
Methods: Commercially available primary, human PAECs were transfected with scrambled control (siCTRL) or gene specific siRNA(s). PAH patient-derived (N=24) and failed donor-derived (N=11) PAECs were obtained from the PHBI. mRNA and protein expression were determined by quantitative RT-PCR and Western blotting, respectively. Cell proliferation was assessed by BrdU incorporation 96h after siRNA transfection. Data was analyzed using t-tests or ANOVA with post hoc pairwise comparisons.
Results: Consistent with our previous findings, CD44 protein expression was increased 4-fold in BMPR2-silenced PAECs 48h following siRNA transfection ($P<0.0001$ vs siCTRL; N=10 unique donors). Genes involved in endothelial-mesenchymal transition and cell proliferation were also increased in BMPR2-silenced PAECs including HMGA1, ID1, SNAI1, and SNAI2 ($P<0.01$ for all vs siCTRL; N=5 independent experiments) and co-silencing CD44 attenuated their upregulation ($P<0.05$ for all vs siBMPR2 alone). Importantly, CD44 knockdown reduced PAEC proliferation in the absence ($P=0.01$ vs siCTRL) and presence of BMPR2 deficiency ($P=0.002$ vs siBMPR2 alone). Like BMPR2-silenced PAECs, CD44 mRNA levels were higher in PAH patient-derived versus failed donor control PAECs ($P=0.07$).
Conclusions: CD44 knockdown corrected aberrant gene expression associated with endothelial-mesenchymal transition and reduced cellular proliferation in BMPR2-deficient PAECs. Thus, endothelial CD44 upregulation may contribute to pathologic vascular remodeling in PAH and represents an unexplored therapeutic target.

Keywords: BMPR2 Deficiency, Endothelial-mesenchymal Transition, Vascular Remodeling

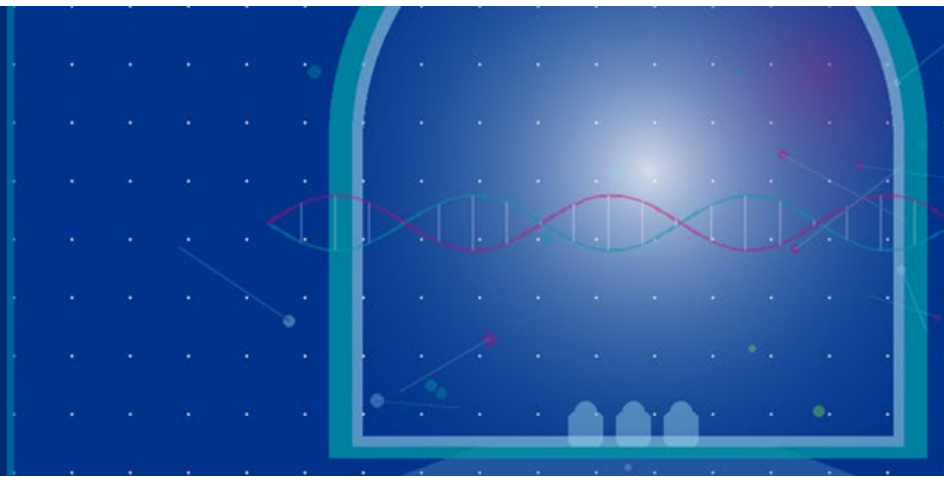


Changes in Perceived Stress Among Women with CVD Risk in Community-Engaged Dietary Behavior Intervention

Siobhan Lawler, IRTA Postdoc, Clinical Center
Mentor: Nicole Farmer
Authors: Siobhan Lawler;* Stephanie Wildridge; Rachel Hingst; Leslie Bardin; Katherine Maki; Samuel Degenhard; Djaina-shae Dervil; Rita Stevens; Alyssa Baginski; Shanna Yang; Sara Turner; Tiffany Powell-wiley; Nicole Farmer

Scientific background: Cardiovascular disease remains the leading cause of death among women, with psychosocial stress recognized as a critical and under-addressed risk factor. Women, particularly those in urban communities, experience disproportionate stress related to caregiving burden, financial strain, and structural inequities, which contribute to elevated cardiovascular disease risk. Community-engaged behavioral interventions may offer scalable strategies to mitigate stress-related cardiovascular vulnerability.
Research question(s)/Hypothesis: We examined whether participation in a community-engaged dietary behavior intervention was associated with a reduction in psychosocial stress across three timepoints. We hypothesized that women would demonstrate significant decreases in perceived stress over the course of the intervention.
Experimental Design/Methodology: DC Cooks is a longitudinal community-engaged dietary behavior intervention occurring over 6 weeks with data collection at baseline and 6-and-12-week post intervention timepoints. Perceived stress was assessed at each time point baseline, mid-intervention, and post-intervention using a validated self-report measure. Linear mixed-effects models were used to evaluate change over time, accounting for repeated measures within participants. Planned contrasts examined differences between timepoints, and a composite stress change score was calculated to quantify overall change.
Results: Participants demonstrated a significant reduction in psychosocial stress across timepoints. Mixed-effects modeling indicated a significant main effect of time, with the greatest reductions observed between baseline and post-intervention. The overall composite stress change score reflected a meaningful decline in perceived stress across the intervention period.
Conclusions and implications: Findings suggest that community-engaged cooking interventions may reduce psychosocial stress among women at risk for CVD. Addressing stress through skill-building, social engagement, and empowerment-based programming may represent an accessible strategy to mitigate women's CVD risk. These results support the integration of dietary behavioral and psychosocial components into chronic disease prevention models targeting women's health.

Keywords: Cardiovascular Disease, Perceived Stress, Women's Health



Characterization of The Senescent Preadipocyte Surfaceome to Target Senescent Cells in Vivo

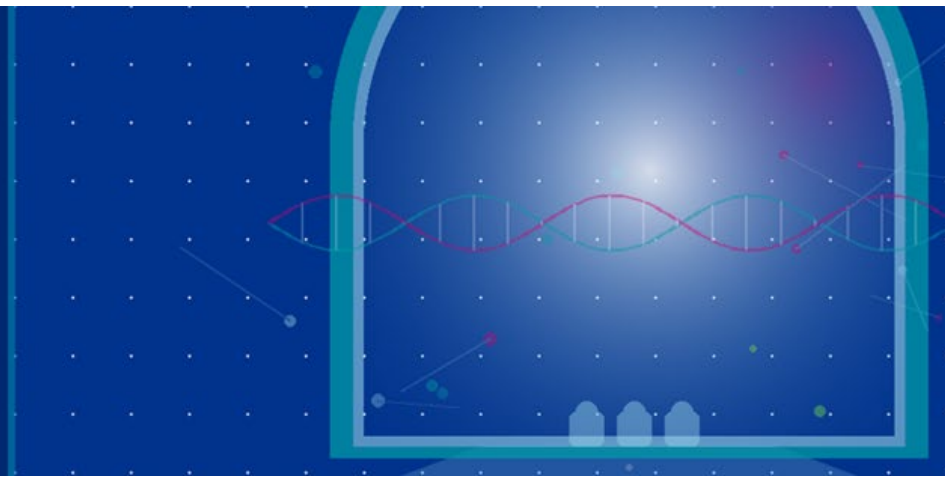
Reema Banarjee, Visiting Fellow, National Institute on Aging

Mentor: Nathan Basisty

Authors: Reema Banarjee;* Amit Dey; Christopher Dunn; Steven Cunningham; Myriam Gorospe; Nathan Basisty

Abstract: Cellular senescence is a complex biological process that drives several aging-associated pathologies. In older women, increased accumulation of senescent cells in adipose tissue has been associated with poor physical function such as low grip strength and gait speed. Developing approaches aimed at selectively identifying and eliminating these cells can be a promising therapeutic strategy for management of age-associated physical decline. Characterization of the senescent cell surface proteome ("Surfaceome") can help identify markers with potential to serve as targets for such senotherapies. To address this, we established a cell culture model of senescence in primary human subcutaneous preadipocytes, which was phenotypically validated using canonical markers like increased levels of CDKN1A, CDKN2A and IL6 mRNAs, and elevated senescence-associated β-galactosidase activity. We applied cell surface capture (CSC) proteomics for the enrichment of surface glycoproteins from senescent and non-senescent control cells, followed by comprehensive proteomic analysis. Data was analyzed using Spectronaut software and an in-house R-based analysis pipeline was utilized to selectively quantify protein expression on the cell surface. Out of the 938 surface proteins identified, 81 were found to be over-expressed on the senescent preadipocyte cell surface when compared to the control cells while 75 proteins were downregulated. Interestingly, several proteins involved in adipose tissue function such as EGFR and ANGPT were found to be downregulated on the surface of senescent preadipocytes. Further, the increased surface abundance of a selective panel of markers was validated via flow cytometry. These markers included novel candidates like CD107 and CD263, as well as DPP4/CD26 that has been previously reported as a surface marker for senescent fibroblasts. Flow cytometry analysis also demonstrated the presence of different sub-populations of senescent cells that showed increased surface abundance of distinct cell surface markers. Immunohistochemistry analysis was used to test the potential of these surface markers to identify senescent cells in vivo using subcutaneous and visceral adipose tissue samples from young and old, lean and obese women. Using these results, we can identify potential new markers for targeted therapy of age-related diseases.

Keywords: Aging, Senescence, Proteomics



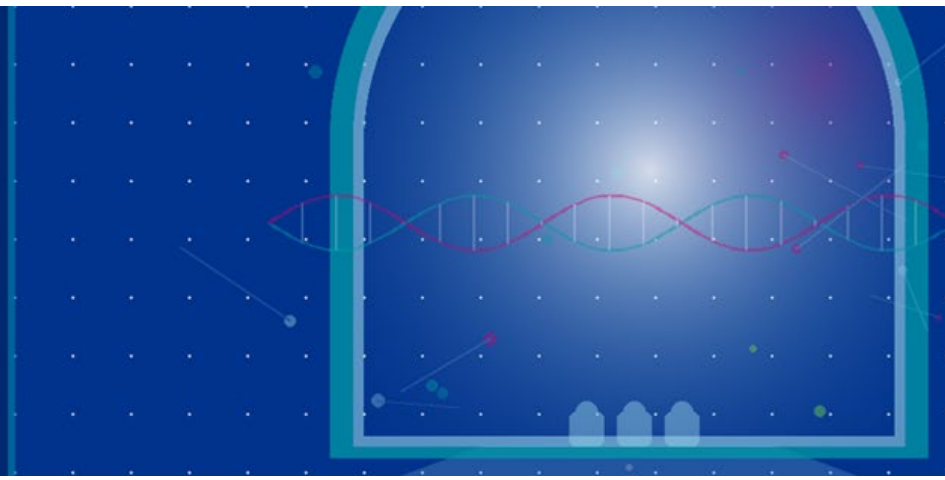
Chronic Pelvic Pain and Quality of Life in Individuals with Mayer-Rokitansky-Küster-Hauser-Syndrome (MRKH): An International Cross-Sectional Survey, *Tadana Vazquez-rothschuh, Research Fellow (MRSP Scholar), Eunice Kennedy Shriver National Institute of Child Health and Human Development*

Mentor: Veronica Gomez-Lobo

Authors: Tadana Vazquez-Rothschuh;* Kirsten Das; Veronica Gomez-Lobo

Abstract: Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is a rare congenital condition characterized by absence or underdevelopment of the uterus, cervix, and upper two-thirds of the vagina in individuals with a 46,XX karyotype, affecting approximately 1 in 4,500–5,000 individuals worldwide. It is classified as Type I (isolated) or Type II, which includes associated renal, skeletal, and auditory anomalies. While the anatomical features are well described, less is known about patient-reported outcomes (PROs). MRKH patients frequently experience psychosocial challenges, including effects on self-esteem and sexual well-being; however, data evaluating quality of life (QoL) and chronic pelvic pain (CPP) remain limited. We aimed to characterize clinical features and PROs among individuals with MRKH to better define disease impact and examine associations between CPP and clinical characteristics, including MRKH subtype and surgical history. We hypothesized that CPP is more prevalent among individuals with MRKH compared to population norms and is associated with greater impairment across QoL domains. This study was part of an IRB-approved cross-sectional questionnaire assessing sexual health and pain among MRKH patients. The survey included demographics, surgical history, dilation practices, and validated measures of sexual health. CPP and QoL were assessed using adaptions of the CPPQ-Mohedo and PROMIS-29 questionnaires. It was disseminated through the BeautifulYou MRKH support group listserv and social media. Inclusion criteria were age ≥18 years and a diagnosis of MRKH. Of 315 participants, 201 completed CPP and QoL sections. Among these, 101 (50.2%) reported CPP. Of those with CPP, 40 (39.6%) had MRKH Type II and 41 (40.6%) had Type I; notably, 65% of individuals with Type II reported CPP. A total of 41 patients (40.6%) reporting CPP had at least one prior surgical procedure. Anxiety demonstrated the greatest QoL impairment, particularly among individuals aged <20 and >50 years. The prevalence of CPP in this cohort exceeds estimates reported in the general population (4-16%), suggesting that CPP may be underrecognized in individuals with MRKH. CPP may substantially impair QoL, underscoring the need for systematic assessment and routinely incorporating PROs into clinical evaluation. Pelvic imaging (MRI) should be considered to identify structural contributors, such as müllerian remnants or endometriosis, enabling more precise and individualized management strategies.

Keywords: MRKH, Quality of Life, Chronic Pelvic Pain

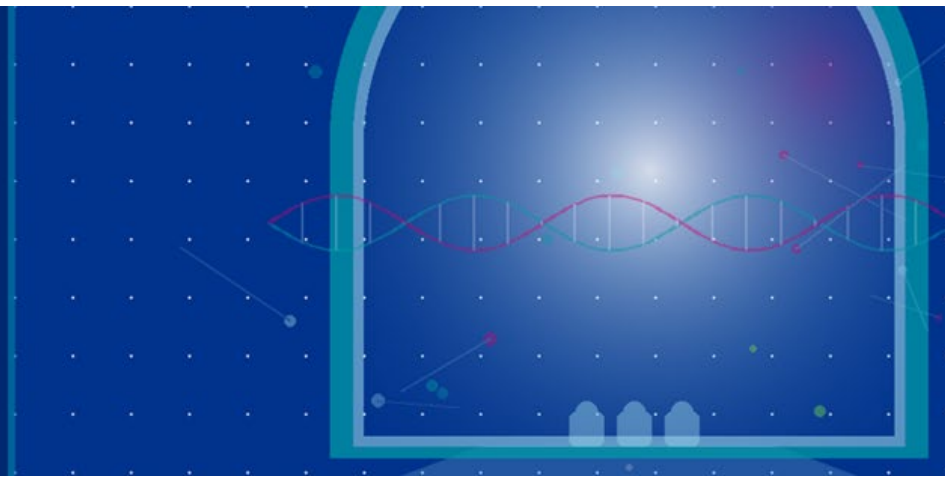


CLIP-HGNN: Graph Neural Network Reasoning Enhances Vision-Language Model Retrieval for Medical Imaging

Zhaohui Liang, Visiting Fellow, National Library of Medicine
Mentor: Sameer Antani
Authors: Zhaohui Liang;* Niccolo Marini; Sivaramakrishnan Rajaraman; Zhiyun Xue; Sameer Antani

Scientific Background: Women face unique diagnostic challenges in chronic conditions including breast cancer, osteoporosis, and cardiovascular disease, where medical imaging is critical for early detection and monitoring. Cross-modal retrieval of radiographs enables clinical decision support and cohort discovery. Vision-language models such as CLIP align images and reports in shared embedding space, but ranking by similarity alone does not capture higher-order relationships among images, reports, and clinical semantics, limiting retrieval quality for cases with subtle imaging patterns.
Research Question and Hypothesis: We hypothesize that explicitly modeling structured relationships among radiographs and reports through heterogeneous graph reasoning can improve medical cross-modal retrieval without retraining the underlying vision-language model by capturing complex semantic relationships that simple similarity metrics miss.
Experimental Design and Methodology: We propose CLIP-HGNN, a graph-based re-ranking framework operating on initial CLIP retrieval. The method constructs a heterogeneous k-nearest-neighbor graph over image and report embeddings and applies relation-aware message passing across modality-specific and clinically grounded node types to refine rankings. We evaluate on chest radiograph retrieval using two large public datasets under within-dataset validation and cross-dataset transfer.
Results: Heterogeneous graph re-ranking consistently improves retrieval quality, with largest gains for text-to-image retrieval and multi-label matching. On smaller datasets, graph reasoning substantially strengthens ranking accuracy; on larger datasets it provides moderate but consistent improvements. Performance gains remain stable under dataset shift, indicating improved robustness versus similarity-based retrieval alone.
Conclusions and Implications: Heterogeneous graph reasoning offers a practical extension to CLIP-based medical retrieval systems, improving ranking quality without altering foundation models. This scalable approach enhances cross-modal retrieval in medical imaging repositories where accurate visual-textual alignment is critical for chronic disease management. The framework's modality-agnostic design makes it applicable to women's health imaging such as mammography, where accurate retrieval supports radiologists in detecting subtle malignancies and tracking disease progression.

Keywords: Graph Neural Networks, Graph Reasoning, Medical Imaging

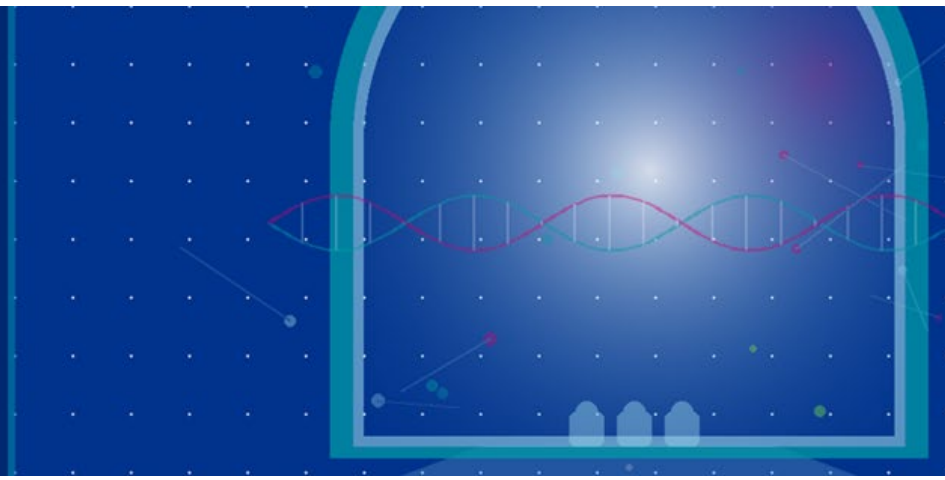


Comorbidities among women diagnosed with gynecologic cancers or benign gynecologic conditions at hysterectomy or bilateral salpingo-oophorectomy

Akemi Wijayabahu, Research Fellow, National Cancer Institute
Mentor: Nicolas Wentzensen
Authors: Akemi T. Wijayabahu;* Rebecca C. Arend; Megan A. Clarke; Gerald Mcgwin; Dhruva Dave; Erin O'connor; Purva Pawar; Ashwini Katre; Angelette M. Edwards; Fibiana A. Oladipo; Jenna R. Logan; Nneka R. Ijeli; Nicolas Wentzensen.

Objectives: The DETECT Study (Discovery and Evaluation of Tests for Endometrial Cancer in Tampons) was designed to identify novel diagnostic and prognostic biomarkers and to evaluate associations with emerging risk factors among women referred to surgery for gynecologic cancer or benign disease. We used the Charlson Comorbidity Index (CCI), a validated tool for assessing comorbidities, to evaluate the distribution and severity of chronic comorbidities among women enrolled in DETECT. Characterizing comorbidity distribution in the DETECT population provides insight into participants' overall health status.
Methods: Women aged ≥18 years undergoing hysterectomy or bilateral salpingo-oophorectomy for endometrial cancer (EC), ovarian cancer (OC), or benign conditions were enrolled in the DETECT Study (July 2019- Dec 2025). Comorbidities present up to five years prior to surgery were identified from electronic medical records using ICD-10 codes. The CCI was calculated with (CCI) and without cancer components (modified CCI) and dichotomized at ≥3, a threshold previously associated with increased mortality. Group comparisons were performed using chi-square tests.
Results: Among 1,123 women, 488 had benign conditions (60% ≥50 years; 30% Black), 553 had EC (93% ≥50 years; 27% Black), and 82 had OC (85% ≥50 years; 21% Black). Among women with EC, the most common non-cancer comorbidities were diabetes (24%) and chronic pulmonary disease (CPD, 14%); for OC, they were diabetes (18%), mild liver disease (18%), and CPD (13%); and for women with benign conditions, diabetes (18%) and CPD (16%) were more prevalent. Among women aged ≥50 years, CCI scores differed significantly across groups, with CCI ≥3 was least common in benign (15%) and more frequent in EC (29%) and OC (44%) ($p<0.001$). After excluding cancer-related conditions, no differences were observed between the three groups ($p \geq 0.05$).
Conclusions: Among women referred for surgery for malignant EC/OC and benign gynecologic conditions, the distribution of non-cancer comorbidities was similar. However, caution is warranted given the potential for misclassification with ICD coding and the limited availability of longitudinal data. Consistent with other studies, common non-cancer comorbidities among women with gynecologic conditions include diabetes and CPD. Further studies are warranted to understand the impact of CCI on outcomes in this study population.

Keywords: Comorbidities, Gynecologic Cancer, Benign Gynecologic Conditions

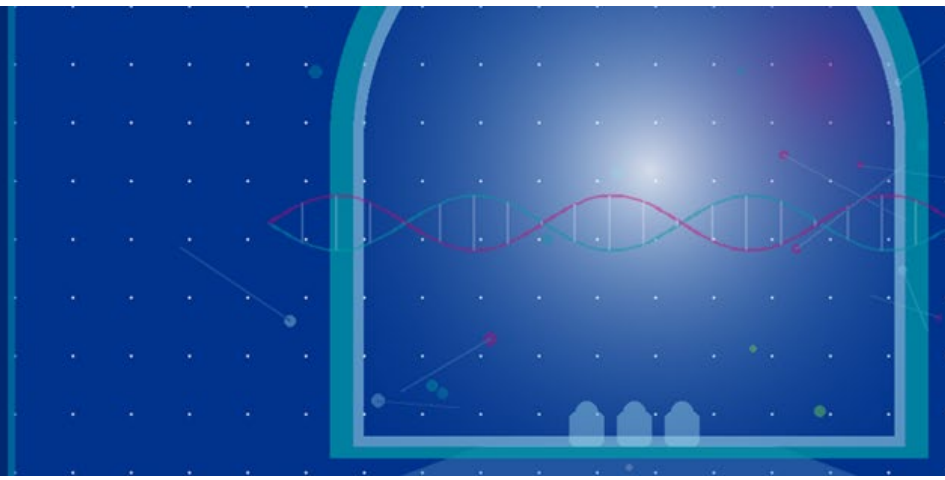


Deciphering Placental Immunity: Predictive Human Placenta Barrier Model to Study Trimester-specific Inflammatory Responses

Justine Noel, IRTA Postdoc, National Center for Advancing Translational Sciences
Mentor: Marc Ferrer
Authors: Justine C Noel;* Yu-chi Chen; Cristina Antich Acedoa; Min Jae Song; Ramkumar Menon; Kyung Sung; Marc Ferrer

Abstract: Placental insufficiency significantly contributes to adverse pregnancy outcomes like intrauterine growth restriction and preeclampsia, impacting global maternal-offspring health and long-term child well-being. To address limitations of 2D models, we developed a robust 3D bio-printed human placenta barrier (hPB) in a multiwell format. This innovative model incorporates primary trophoblasts, endothelial cells, placental fibroblasts, and pericytes, accurately recapitulating hPB structure and function at early and late gestational stages. We induced placental inflammation by apically exposing models to 500 ng/mL Lipopolysaccharide (LPS) or 10µg/mL PolyI:C for 24 hours. The treatments revealed distinct, term-specific responses: early-term trophoblasts showed a compensatory response with enhanced nutrient transport and preserved barrier integrity. Conversely, late-term trophoblasts exhibited decreased hormone production, increased inflammation, and compromised barrier integrity, suggesting in-utero exposure to harmful substances. Importantly, Poly(I:C) exposure, mimicking viral infection, significantly upregulated IL-6 production in healthy and immortalized cells. As IL-6 is a key pro-inflammatory cytokine of the pre-eclamptic trophoblasts, our model faithfully emulated the inflammatory responses in preeclampsia. This physiologically relevant models allows mechanistic dissection of inflammatory pathways and identification of therapeutic targets. Ongoing analysis of differentiation capacity and computational analysis of the vascular network will enhance understanding of hPB dynamics. Our adaptable 96-well format enables high-throughput drug screening to modulate detrimental LPS/PolyI:C effects. Ultimately, this research aims to improve maternal and offspring health by advancing understanding of hPB function across gestation, leading to novel diagnostics and targeted therapies.

Keywords: Maternal-fetal Immunity, Maternal Health, Placental Immunity

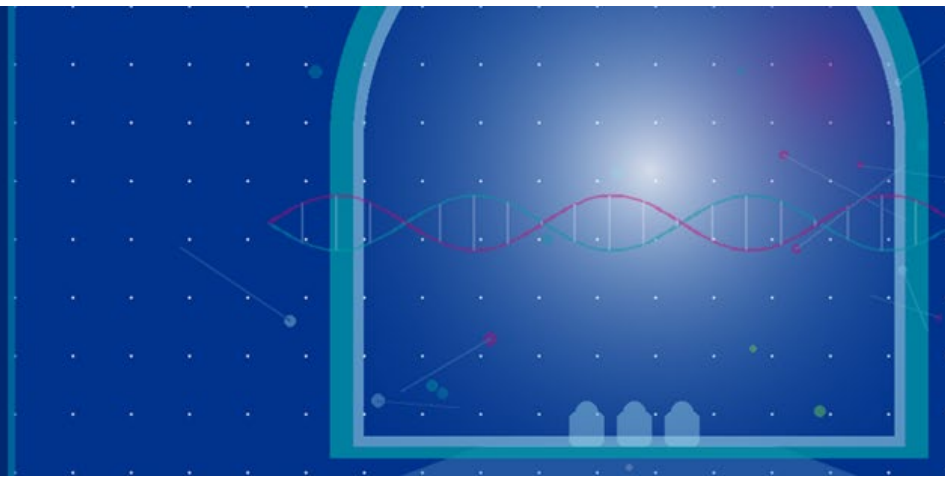


Decoding Estrogen Receptor Responses to Ultradian, Circadian, and Infradian Hormone Dynamics: Implications Women's Health

Diana Stavreva, Staff Scientist, National Cancer Institute
Mentor: Gordon Hager
Authors: Diana Stavreva;* Kaustubh Wagh; Le Hoang; Hannah Lapoint; Sohyoung Kim; Louis Schiltz; Arpita Upadhyaya; Rajagopal Chari; Gordon Hager

Scientific Background: Estrogen receptor alpha (ERα) is a key regulator of female reproductive development and a major driver of breast cancer and other women's health–related chronic conditions. Circulating estradiol (E2) levels fluctuate across multiple physiological time scales, including hourly ultradian pulses, daily circadian rhythms, and the monthly infradian ovarian cycle. While hormone dynamics are known to influence glucocorticoid receptor signaling, how ERα interprets these temporal patterns remains poorly understood.
research Question/Hypothesis: We hypothesized that ERα decodes ultradian, circadian, and infradian hormone dynamics in a manner distinct from other steroid receptors, resulting in unique transcriptional outputs that may influence chronic disease risk and therapeutic responses in women.
Experimental Design/Methodology: Using single-molecule tracking in living MCF7 cells combined with imaging, biochemical assays, and RNA sequencing, we examined ERα–ligand interaction dynamics and transcriptional responses under controlled ultradian E2 pulses, circadian synchronization, and simulated follicular and luteal phase hormone conditions (E2 alone versus E2 plus progesterone, P4).
Results: In contrast to glucocorticoid receptor signaling, which exhibits pulsatile transcription in response to ultradian hormone exposure, ERα formed stable interactions with E2 and sustained continuous transcription even under discontinuous E2 stimulation. Circadian synchronization using transient glucocorticoid receptor activation transiently altered early responses of co-regulated genes; however, ER-dependent transcription was largely uniform across subsequent circadian phases. Modeling the infradian cycle revealed marked differences between follicular and luteal phases, with a subset of genes preferentially responding to combined E2 and P4 exposure.
Conclusions and Implications: ERα integrates hormone signals differently across physiological time scales, showing resilience to ultradian and circadian fluctuations but distinct transcriptional remodeling across the ovarian cycle. These results have important implications for hormone replacement strategies, breast cancer biology, and other estrogen-driven chronic conditions in women, emphasizing the need to consider hormone timing in therapeutic design.

Keywords: Steroid Hormone Signaling, Hormone Dynamics, Transcription Regulation, HRT

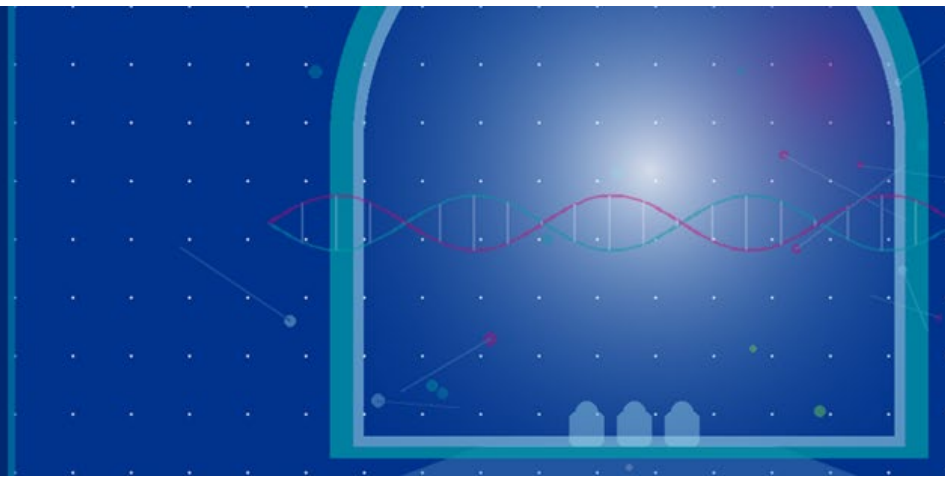


Development of An Exercise Question Prompt List (QPL) For Breast Cancer Survivors

Oliver Wilson, IRTA Postdoc, National Institute on Minority Health and Health Disparities
Mentor: Jinani Jayasekera
Authors: Oliver Wilson;* Tara Sanft; Isaac Ergas; Jacob Schnieder; Yuru Huang; Gisela Butera; Quynh Nguyen; Brenda Curtis; Richard Street; Jinani Jayasekera

Background: High-quality communication about exercise during clinical visits may increase participation among breast cancer survivors. However, survivors' exercise participation and communication preferences remain poorly understood. The aim of this study was to develop an exercise-focused question prompt list (QPL) to identify survivors' participation and communication preferences, and facilitate exercise discussions, prescriptions, and referrals through shared-decision making and autonomy.
Materials and Methods: First, a systematic scoping review was conducted following PRISMA-ScR guidelines. Five databases were searched for articles reporting breast cancer survivors' exercise participation and communication preferences worldwide in between 01/2005-07/2025. Survivor characteristics and exercise preferences were extracted and used to draft a QPL. Weighted average percentages were calculated. Experts (n=10) provided feedback via interviews, and the QPL was revised accordingly.
Results: Our review included 29 studies. Overall, preferences were found for exercise frequency (77.6%:≥2 sessions/week), intensity (63.1%:moderate-intensity), and duration (62.9%:30-60 minutes/session), variety (68.3%), and time of day (52.4%:morning). Preferred locations included home (29.3%), community recreation facilities (32.9%), and outdoors (31.4%). Supervised exercise (53.4%) and exercising with others (57.7%) were preferred over unsupervised exercise (35.2%) and exercising alone (34.4%), respectively. Survivors preferred exercise counseling/advice from an exercise specialist (59.3%) and face-to-face delivery (63.7%). Experts viewed the QPL favorably and recommended modifications to improve comprehension and additional questions on willingness to pay and travel for exercise, and interest in diet/nutrition information.
Conclusions: Survivor preferences and expert input are reflected in the novel QPL. With further testing, the QPL may support delivery of exercise information aligned with exercise/survivorship guidelines. Future research should evaluate the QPL's impact on survivors' exercise participation and psychological antecedents to exercise (e.g., self-efficacy, goal setting).

Keywords: Exercise, Communication, Patient Preference



Discovery of First-in-Class Selective Small-Molecule Agonists of the Relaxin/Insulin-like Family Peptide Receptor 2 (RXFP2) and their therapeutic potential in bone metabolism

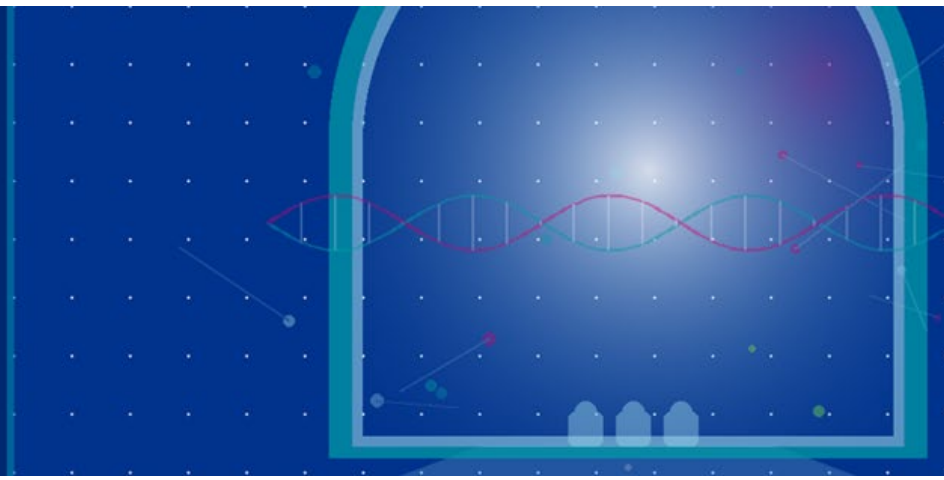
Konstantinos Afratis, IRTA Postdoc, National Center for Advancing Translational Sciences

Mentor: Juan Marugan

Authors: Konstantinos Afratis,* Kenneth Wilson, Maria Esteban-Lopez, Courtney Myhr, Wenjuan Ye, Curtis Moore, Noel Southall, Xin Hu, Abhijeet Kapoor, Christopher Leclair, Samuel Kotler, Pranav Shah, Elias Carvalho Padilha, Yuhong Fang, David Calabrese, Emmett George, Amy Wang, Xin Xu, Elena Barnaeva, Marc Ferrer, Mark Henderson, Irina Agoulnik, Alexander Agoulnik, Juan Marugan

Abstract: The insulin-like 3 (INSL3)/RXFP2 signaling pathway is a critical regulator of physiological processes, including bone metabolism. While recombinant INSL3 peptide has shown therapeutic potential for bone remodeling, its clinical utility is limited by a short half-life and the requirement for intravenous administration. The development of potent, selective, and orally bioavailable small-molecule RXFP2 agonists is essential for probing INSL3 biology and developing novel treatments for conditions such as osteoporosis. We have identified and optimized the first potent, selective, and orally bioavailable small-molecule agonists for RXFP2. Compound 68 serves as a robust preclinical lead candidate to evaluate the therapeutic benefits of RXFP2 activation in bone remodeling and other INSL3-related physiological systems. These molecules provide a powerful new toolset for the transition from peptide-based to small-molecule-based modulation of the relaxin family receptors.

Keywords: Relaxin, Osteoporosis, Bone Metabolism

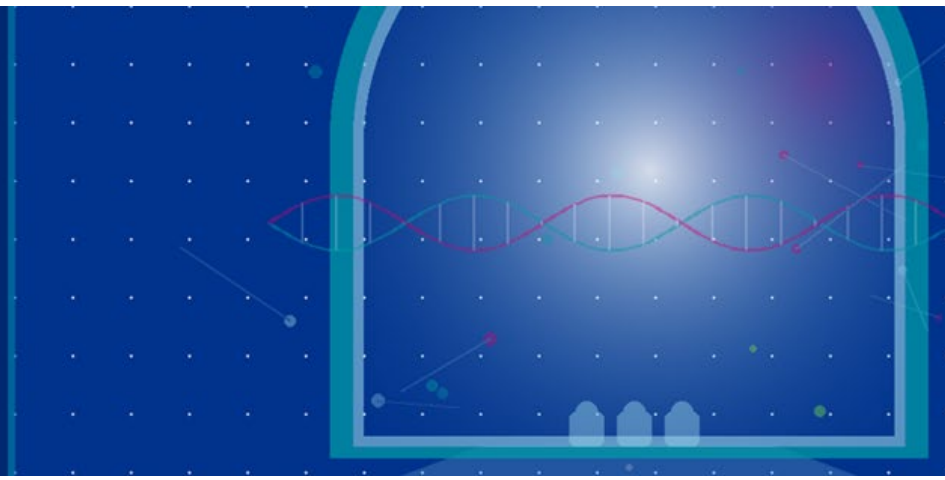


Donor-specific Digital Twin for Living Donor Liver Transplant Recovery

Suvankar Halder, Visiting Fellow, National Institute of Diabetes and Digestive and Kidney Diseases
Mentor: Vipul Periwal
Authors: Suvankar Halder;* Vipul Periwal

Abstract: Living donor liver transplantation (LDLT) is a life-saving procedure for recipients, but its long-term success depends on the donor liver's ability to regenerate after surgery. U.S. registry data from 2002–2021 indicate that women comprise a slightly higher proportion of living liver donors, whereas men are more frequently transplant recipients. In living donors, post-surgical liver regeneration is a highly coordinated process that restores liver mass and function, but donor heterogeneity leads to substantial variability in recovery trajectories, underscoring the need for individualized monitoring strategies. With the rising global burden of liver disease, ensuring donor safety and optimizing post-surgical outcomes are more important than ever. Existing clinical markers provide only limited, static assessments and lack predictive power for personalized recovery management. To address this gap, we developed the Personalized Progressive Mechanistic Digital Twin (PePMDT)-a deep learning–based framework that integrates mechanistic mathematical modeling with gene expression data to predict donor-specific recovery dynamics. We analyzed whole-transcriptome RNA sequencing data from 12 healthy LDLT donors (6 male, 6 female), collected across 14 time points over one year. Weighted Gene Co-expression Network Analysis identified liver resection–associated transcriptional programs, which were organized into distinct gene clusters with characteristic temporal dynamics. These clusters were mapped to a validated mechanistic model of liver regeneration using deep learning, enabling construction of a patient-specific digital twin of post-donation recovery. PePMDT accurately predicted individual recovery trajectories, demonstrating the ability to translate blood-derived gene expression profiles into dynamic regenerative responses. This framework provides a quantitative approach for tracking and forecasting donor-specific post-surgical outcomes by linking molecular data to computational liver models. While digital twins are increasingly used in medicine, their application to regenerative biology remains limited. Our results establish PePMDT as a disease-specific digital twin for LDLT, offering a continuous, mechanistic, and predictive tool for precision medicine. By accounting for donor heterogeneity, including sex-related biological variation, PePMDT provides a precision medicine tool relevant to women's health, enabling safer donation and improved post-surgical monitoring.

Keywords: Digital Twin, Living Donor Liver Transplant (LDLT), Liver Regeneration, Deep Learning



Drinking Water Contaminants in Community Water Systems and Risk of Breast Cancer in the California Teachers Study Cohort

Lydia Post

Mentor: Rena Jones

Authors: Lydia Marcus Post;* Maya Spaur; Laura E. Beane Freeman; Jared A. Fisher; Alexander P. Keil; Emma S. Spielfogel; Komal Bangia; James V. Lacey, Jr.; Mary H. Ward; Gretchen Gierach; Rena R. Jones

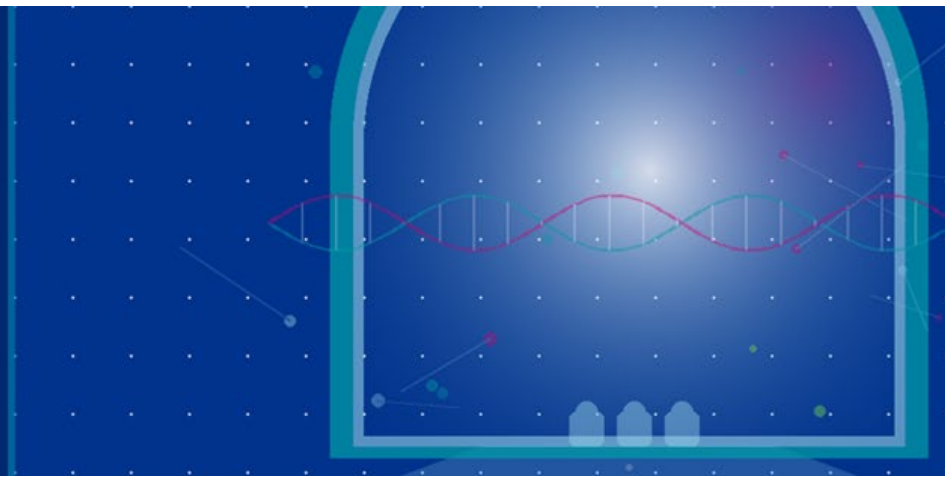
Purpose: Many drinking water contaminants are known or suspected carcinogens and some are endocrine disrupting, but few epidemiologic studies have evaluated their associations with breast cancer risk. We sought to investigate these relationships in a US-based cohort.

Methods: We assessed long-term average (1990-2005) concentrations of individual and total trihalomethanes (TTHMs), nitrate, arsenic, and uranium in community water systems that served enrollment addresses in the California Teachers Study, a cohort of female educators enrolled 1995-1996 with follow-up through 2020. Our analytic sample (N=68,055) was cancer-free at enrollment and lived >10 years at their address. We used Cox models to estimate hazard ratios and 95% confidence intervals (HRs [CIs]) across categories (quartiles/90th percentile) for associations with breast cancer overall (N=6,749), by disease extent (in situ [19%] or invasive tumors [81%]) and estrogen receptor (ER) status (ER+ 73%, ER- 12%). We adjusted for age, body mass index, first degree family history of breast cancer, and neighborhood socioeconomic status. We evaluated a mixture effect via quantile-based g-computation.

Results: Higher average TTHM levels were positively associated with breast cancer risk overall (HR>90vs<25th=1.08 [0.99-1.18], ptrend<0.01) and with invasive (HR=1.06 [0.96-1.18], ptrend=0.01) and ER+ (HR=1.13 [1.02, 1.25], ptrend<0.01) tumors, but we found no clear relationship with in situ (HR=1.13 [0.93-1.37], ptrend=0.13) or ER- (HR=1.05 [0.82-1.36], ptrend=0.87) tumors. Among THMs, bromoform was associated with overall breast cancer, invasive, and ER+ tumors (ptrend<0.05), and chloroform with ER+ tumors (ptrend=0.01). We found no relationships with arsenic, nitrate, or uranium. An interquartile range increase in the contaminant mixture was associated with invasive (HR=1.10 [1.00-1.21]) and ER+ (HR=1.07 [0.97-1.19]) tumors; TTHM was the main contributor. We saw no associations for in situ (HR=0.91 [0.74-1.11]) or ER- (HR=0.95 [0.74-1.22]) disease.

Conclusions: We found that THMs were associated with increased breast cancer risk, with potential differences by disease extent and ER status. Further investigation into these exposures as potentially modifiable risk factors for breast cancer is warranted.

Keywords: drinking water contaminants, disinfection byproducts, breast cancer



Evaluating Coronary Heart Disease Risk Classification Among Black and Hispanic/Latina Women: The All of Us Research Program

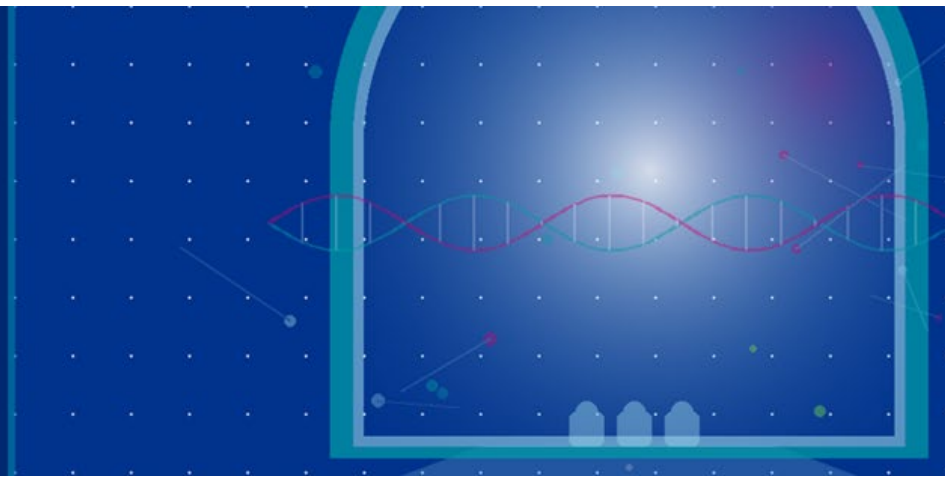
Christy Rodriguez, External Trainee Under Excellence in Mentorship for Unity, Resilience, and Growth (EMURG) Mentorship Program at Johns Hopkins, Clinical Center

Mentor: Lena Lee

Authors: Christy Rodriguez;* Daniel Simmonds; Aysha Jawed; Kathryn Van Eck; & Harolyn Belcher

Abstract: Coronary heart disease (CHD) is the leading cause of illness and death among US women, with racial and ethnic disparities in risks and outcomes. The atherosclerotic cardiovascular disease (ASCVD) risk estimator is the clinical standard; however, it may overestimate risk, and its validity in Black and Hispanic/Latina women is unclear. We assessed how ASCVD risk factors relate to cardiovascular outcomes based on the social construct of race/ethnicity. Using the All of Us Research Program (oversampled Black and Hispanic/Latina populations), we analyzed electronic medical record diagnoses from 355,849 women: 222,243 White (62.5%), 58,959 Black (16.6%), and 74,647 Hispanic (21.0%). Outcome variables were hypertension (an ASCVD risk factor) and myocardial infarction (MI; an ASCVD outcome); comparisons used two-sample tests of proportions with chi-square tests. Hypertension prevalence was 20.9% in White women (n=46,380), 20.1% in Hispanic women (n=15,021), and 35.1% in Black women (n=20,679). MI prevalence was similar for White (1.83%; n=4,058) and Hispanic women (1.82%; n=1,355; χ^2=0.03, p=0.86) but higher among Black women (3.53%; n=2,080; χ^2=631.36, p<0.001). Hypertension was associated with higher MI prevalence in White (2.80% vs 1.57%; χ^2=307.3, p<0.001) and Hispanic women (2.08% vs 1.75%; χ^2=7.05, p=0.008), but not Black women (3.52% vs 3.53%; χ^2=0.002, p=0.96). Despite a higher hypertension/ASCVD burden in Black women, hypertension diagnosis was not a significant risk factor. Although MI rates were similar in Hispanic and White women, hypertension was a stronger predictor in White women, supporting group-specific risk contributions and the need for further evaluation of ASCVD equation sensitivity, specificity, and validity across the sociopolitical exposure and constructs of race/ethnicity.

Keywords: Coronary Heart Disease (CHD), *All of Us* Research Program

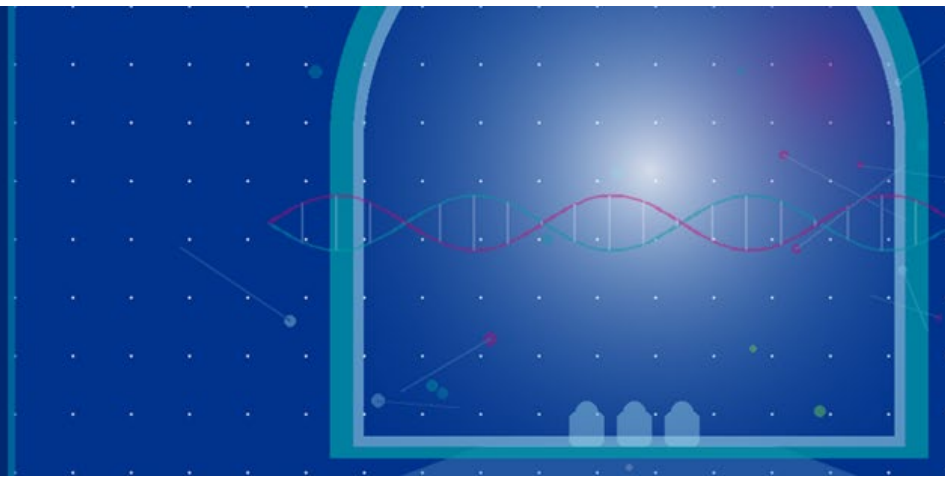


Exercise Decreases Multiple Sclerosis Progression Slopes, More Profound in Males

Amir Moghadam Ahmadi, Staff Clinician, National Institute of Allergy and Infectious Diseases
Mentor: Bibiana Bielekova
Authors: Amir Moghadam Ahmadi;* Peter Kosa; Marie Kanu; Yolanda Mejia; Bibiana Bielekova

Background: Growing evidence suggests that exercise benefits central nervous system (CNS) integrity and slows disability progression in people with multiple sclerosis (pwMS), likely through neuroprotective mechanisms. We aimed to independently replicate this data by studying association between self-reported exercise and MS progression rates, as well as comparing this association between different sex and age groups.
Methods: We developed a questionnaire assessing exercise and manual work intensity and frequency across four age periods (0–18, 19–30, 31–50, >50 years). Responses were integrated into ordinal exercise scores. In 177 pwMS who completed the questionnaire, rates of disability progression were quantified using linear regression models of Combinatorial Weight-Adjusted Disability Scale (CombiWISE) scores measured over median of 7 visits spanning 6.07 years. The primary analysis examined associations between current exercise and CombiWISE slopes, adjusting for sex, disease duration (DD), MS subtype, and BMI. Sensitivity analyses assessed effects on cross-sectional MS severity measures: CombiWISE/Age, CombiWISE/DD, and brain damage severity (MRI + SDMT outcomes/Age).
Results: Exercise intensity and duration declined with age and disability. Males reported higher early-life exercise levels, leading to steeper declines over time. Greater current exercise was significantly associated with slower CombiWISE progression ($p = 0.0006$), lower CombiWISE/Age ($p = 0.017$), lower CombiWISE/DD ($p = 0.004$), and reduced brain damage severity ($p = 0.043$). Associations were consistent across MS subtypes and age groups, with the strongest effects in patients with MS onset between ages 19–30.
Conclusions: Higher physical activity is linked to slower accumulation of physical and cognitive disability in pwMS.

Keywords: Multiple Sclerosis, Exercise, Disability

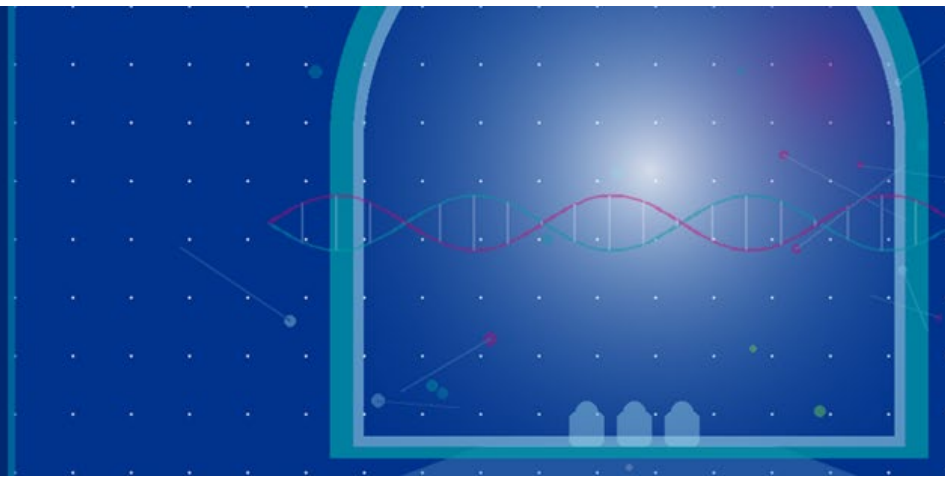


Exploring Design Principles That Govern the Formation of Extremely Stable Peptide-based Polyelectrolyte Complex Nanoparticles for Drug Delivery

Nichole O'neill, CRTA, National Cancer Institute
Mentor: Joel Schneider
Authors: Nichole O'neill;* Tuan Samdin; Caleb Anderson; Joel Schneider

Abstract: Potential therapies in preclinical development with poor physiochemical properties, i.e., low aqueous solubility or cell permeability, are typically disregarded, but can be rescued through use of appropriate delivery devices. We are developing peptide-based polyelectrolyte complex nanoparticles (PEC NPs) for the delivery of small molecule and peptide drugs. These particles are formed by flash nanocomplexation where oppositely charged peptide amphiphiles are rapidly mixed in a confined impinging jet mixer. However, peptide-based PEC NPs have yet to be reported and the molecular design principles governing their formulation are unknown. We comprehensively examined over 60 peptide systems to define the critical attributes leading to stable particle formation, namely: electrostatics, hydrophobicity, β-sheet propensity, aromaticity, side chain length, turn motif identity, and chirality. We expected that electrostatics would be the primary driving force for peptide complexation leading to stable particle formation since the first mechanistic step in assembly is charge neutralization. Surprisingly, we find that peptide hydrophobicity is the main determinant to facile complexation and particle stability. Calculated peptide hydrophobicity scores show a positive correlation with particle parameters that reflect a stable colloidal system, such as zeta potential and scattering correlation coefficient. However, peptides with extremely high hydrophobic content self-aggregate indicating that an optimal hydrophobic content exists for these systems that cannot be exceeded. Additionally, the inclusion of strong β-turn motifs and sequences of high β-sheet propensity is important. Strong turn motifs may restrict the assembly pathway resulting in highly ordered sheet-rich particles. As such, extremely stable and well-defined particles can be formed by the complexation of oppositely charged, turn-containing, phenylalanine-rich amphiphiles where hydrophobicity is balanced with aromaticity. These foundational findings enable the development of a general peptide nanoparticle platform to deliver small molecule and peptide drugs.

Keywords: Biophysics, Nanoparticles, Spectroscopy



Ezrin plays a key role in regulating the viscoelastic properties and force generation in T lymphocytes during the formation of the immunological synapse

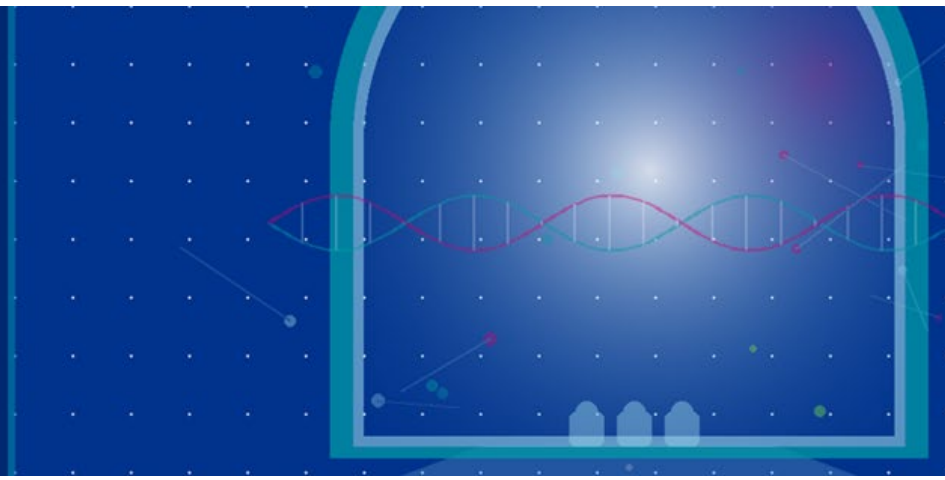
Mazen Mezher, IRTA Postdoc, National Institute of Biomedical Imaging and Bioengineering

Mentor: Alexander Cartagena- Rivera

Authors: Mazen Mezher;* Kun Do; Mohanish Chandurkar; Alexander Zhovmer3; Erdem Tabdanov; Sangyoon Han; Alexander Cartagena-rivera.

Abstract: The immunological synapses (IS), which are the interface between a T lymphocyte and an antigen-presenting cell, plays a crucial role in T cell activation. This process begins when the T-cell receptor (TCR) binds to its specific antigenic peptide. Several studies have highlighted that the mechanical properties of T cells during activation significantly impact various cellular functions, including proliferation, migration, and cytotoxic activity. The formation and maintenance of the IS are facilitated by force generation through the dynamic interaction of the actomyosin and microtubule cytoskeletal networks. However, the precise way in which force generation influences the mechanical properties of T cells remains unclear. In our study, we utilized high spatiotemporal resolution Atomic Force Microscopy (AFM) to measure the viscoelastic response of T cells through common mechanical parameters (storage and loss moduli) across different timescales at the nanometer scale. Additionally, we used Traction Force Microscopy (TFM) to quantify the traction stresses generated by T cells on soft silicone hydrogels during IS formation. Our findings reveal that T cells exhibit structurally diverse viscoelastic properties at the nanoscale during IS formation, triggered by CD3/CD28/LFA-1 co-stimulation. Specifically, we observed significantly higher elastic and viscous properties at the edge and center of the IS, while the peripheral transition region appeared softer and more fluid. These observations correspond to changes in the actomyosin cytoskeleton structure in these areas. Furthermore, our results demonstrated that perturbations in cytoskeletal proteins regulating filamentous actin caused substantial changes in T cell elasticity and fluidity, as well as alterations in the traction stresses generated during IS formation. Notably, we saw significant softening, fluidization, and a decrease in traction stresses when detaching the actin cortex from the plasma membrane by inhibiting Ezrin activity. In summary, understanding the relationship between key cytoskeletal structures at the IS and the mechanical property of the cell is essential for maintaining and forming the IS, offering valuable insights into potential strategies to engineer T cells with enhanced activation and cytotoxic abilities.

Keywords: immunological synapses (IS), traction stresses, viscoelastic response, force generation, Traction Force Microscopy (TFM), Atomic Force Microscopy (AFM)

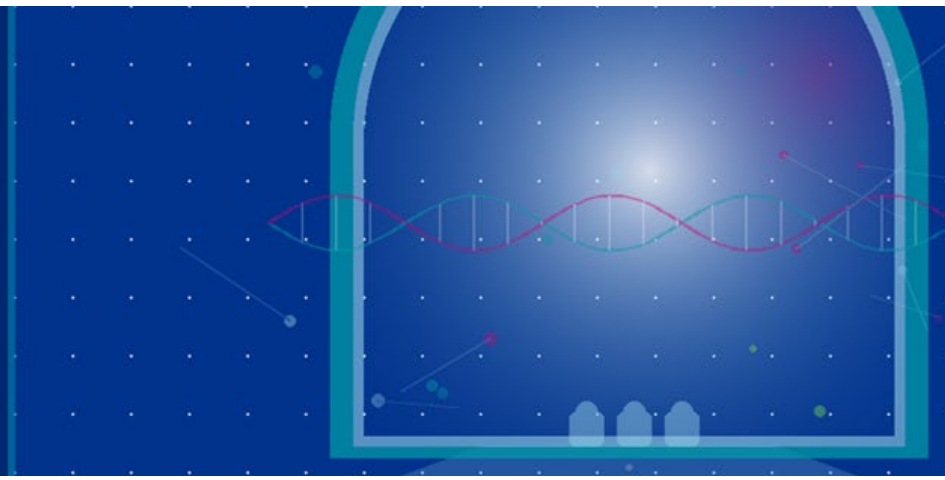


Female Mice Are More Susceptible Than Males to Decline in Social Memory Ability Across Age

Sarah Williams Avram, Staff Scientist, National Institute of Mental Health
Mentor: Scott Young
Authors: Sarah Williams Avram;* Rahul Chaturvedi, Scott Young

Abstract: Age-related cognitive decline exhibits sex-specific patterns, yet social memory, an essential component of adaptive behavior, remains underexplored in preclinical models the of women's health. This study investigated the effects of age and sex on social memory performance in mice to better understand biological mechanisms that may contribute to sex-specific vulnerability to cognitive aging. Young adult (3–5 months) and aged (18–22 months) male and female C57BL/6J mice were assessed using a validated social recognition paradigm. Mice were exposed to a novel conspecific and re-exposed following a 30-minute retention interval to evaluate recognition memory. Investigation time toward familiar versus novel conspecifics served as the primary outcome measure. Locomotor activity was measured to control for non-mnemonic confounds. Young mice of both sexes demonstrated robust social recognition, indicated by reduced investigation time upon re-exposure. In contrast, aged mice exhibited significant impairments in social memory; however, the magnitude and pattern of decline differed by sex. Aged females were more likely to show a pronounced reduction in discrimination between familiar and novel conspecifics compared to aged males. These deficits were not attributable to alterations in locomotion or baseline sociability. Interestingly, within the aged cohort, approximately one-third of subjects maintained high performance on the social memory task. This indicates a high variability among subjects. These findings reveal sex-dependent trajectories of social cognitive aging, with aged females exhibiting heightened vulnerability to social memory impairment. Given the increased risk of age-associated cognitive disorders among women, understanding sex-specific neural mechanisms underlying social memory decline may inform targeted prevention and therapeutic strategies. This work underscores the importance of incorporating sex as a biological variable in preclinical models of cognitive aging relevant to women's health.

Keywords: Social Memory, Aging, Vasopressin



From Weak to Strong: a Novel Role of Mot1 in Choreographing TBP Dynamics To Balance Gene Expression During Stress

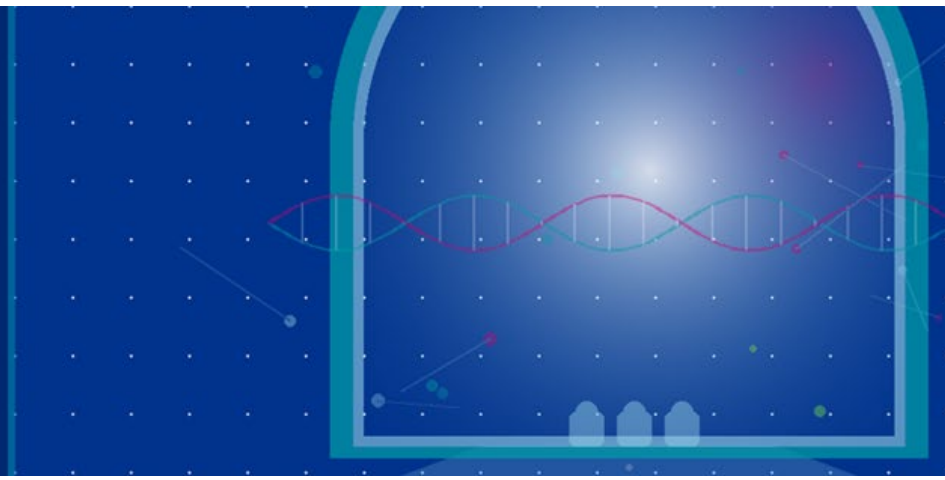
Priyanka Mittal, Visiting Fellow, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Mentor: Alan G Hinnebusch

Authors: Priyanka Mittal;* Alan G Hinnebusch

Abstract: Recruitment of TATA-binding protein (TBP) to RNA Polymerase II core promoters is essential for PIC (preinitiation complex) assembly at nearly all genes, facilitated in budding yeast by coactivator complexes SAGA and TFIID. It is thought that SAGA recruits TBP to promoters of stress-responsive genes with consensus (strong) TATA sequences, while TFIID is more involved with housekeeping genes containing non-consensus (weak) TATA-like sequences. Yeast Mot1 is a DNA-dependent ATPase that dissociates TBP from incomplete PICs in vitro but its role in regulating gene expression in vivo is incompletely understood. Previous studies indicated that Mot1 favors TFIID-dependent promoters by preferentially dissociating TBP from SAGA-regulated genes. While it was suggested that TBP bound to DNA in association with TFIID is less accessible to Mot1 compared to TBP delivered by SAGA, a structure of the TBP-TFIID-TFIIA-DNA complex revealed only indirect interaction between one TFIID subunit (Taf4) and TBP bridged by TFIIA. It is unclear therefore how Mot1 differentiates between SAGA and TFIID-dependent promoters for stable TBP-DNA binding. To better understand Mot1's role under stress, we conducted ChIP-Seq analysis to determine the effect of depleting Mot1 from nuclei on TBP binding at genes activated by transcription factor Gcn4 under amino acid starvation. Unlike previous findings in non-stress conditions, we discovered that Mot1 is necessary for strong TBP binding at highly activated Gcn4 target genes. Mot1 depletion also reduced TBP binding at other highly expressed genes transcribed constitutively while increasing TBP occupancies at weakly expressed genes, regardless of whether they rely on SAGA or TFIID in non-stressed cells. A similar pattern was found for genes highly induced by oxidative stress, which are not activated by Gcn4. Interestingly, while Mot1 depletion reduced TBP binding at highly expressed stress-induced and housekeeping genes alike, transcription (measured by RNA Pol II binding and RNA-Seq) declined only at TFIID genes. This suggests that transcription of stress-activated genes regulated by SAGA can proceed normally at reduced TBP occupancies. Our study reveals that Mot1 helps redistribute TBP from weakly- to strongly-expressed genes during stress rather than simply shifting TBP from SAGA- to TFIID genes. We further suggest that stress-responsive genes have a unique mechanism allowing them to maintain robust transcription at reduced TBP binding.

Keywords: Mot1, TATA, TBP, starvation conditions



Genetic Influence on Blood Pressure Trajectory During Pregnancy

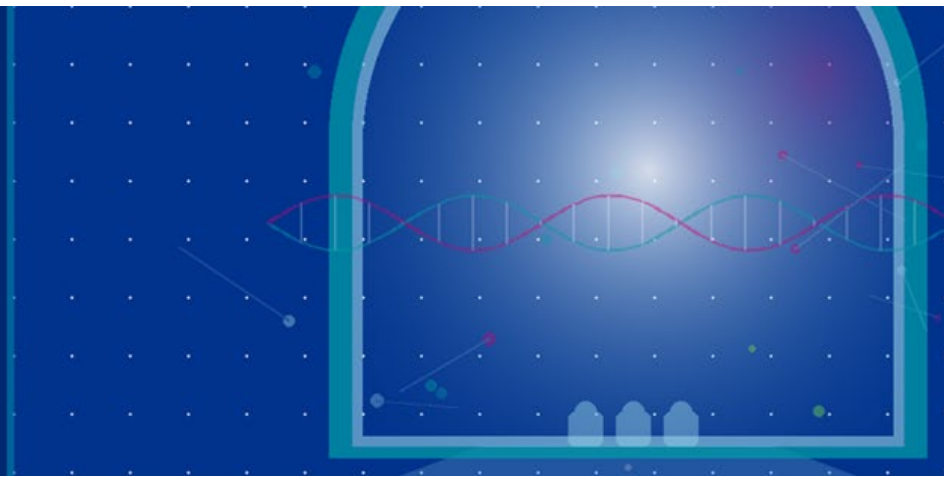
Prabhavi Wijesiriwardhana, Visiting Fellow, Eunice Kennedy Shriver National Institute of Child Health and Human Development

Mentor: Fasil Tekola-ayele

Authors: Prabhavi Wijesiriwardhana;* Guisong Wang; Tesfa Dejenie Habtewold; Kunal Kathuria; Fasil Tekola-ayele

Abstract: Maternal blood pressure (BP) has a unique trajectory during pregnancy, with levels typically dropping until mid-pregnancy and then rising until delivery. The change in BP during gestation signals maternal circulatory adaptive response, and has been linked to pregnancy complications including preeclampsia, placental abruption, preterm birth, and low birth weight. Genome-wide association studies have identified hundreds of genetic loci associated with BP in adults; however, the genetic underpinnings of BP trajectory during pregnancy are unknown. We aimed to identify maternal genetic loci associated with the prenatal trajectory of four BP traits (systolic BP, diastolic BP, mean arterial pressure, and pulse pressure). Data included pregnant woman with at least 3 measurements of systolic and diastolic BP in two pregnancy cohorts (total N=7,646; 36,868 BP measurements). Pulse pressure and mean arterial pressure were calculated from systolic and diastolic BP using standard methods. To identify genetic variants that shift the mean BP trait trajectory and the intra-individual variability in BP trait trajectory, genome-wide analyses were performed in each cohort using a linear mixed effects-based model adjusted for maternal age, parity, and genotype principal components, with varying slope for gestational week at BP measurement. Results were combined by meta-analyses. We identified 41 loci associated with variability in trajectory of diastolic BP, 38 loci for systolic BP, 91 loci for mean arterial pressure, and 1 locus for pulse pressure ($p < 5x10-8$). At least eleven loci were shared by two or more BP traits. Genes linked to variability in diastolic BP and mean arterial pressure trajectories showed marked upregulation in heart left ventricle, while systolic BP–associated genes were downregulated in tibial artery, suggesting tissue-specific regulation of blood pressure components. Several loci have previously been associated with traits related to blood pressure, lipid traits, and fetal growth. It is possible that genetic loci regulate intra-individual variability in BP during pregnancy through their influence on women's cardiovascular and other physiological adaptations across gestation. These findings would help in identifying new biological pathways in blood pressure regulation with potential for improved cardiovascular disease prevention for the mother and child.

Keywords: Blood Pressure Trajectory, Pregnancy, Genetic-loci

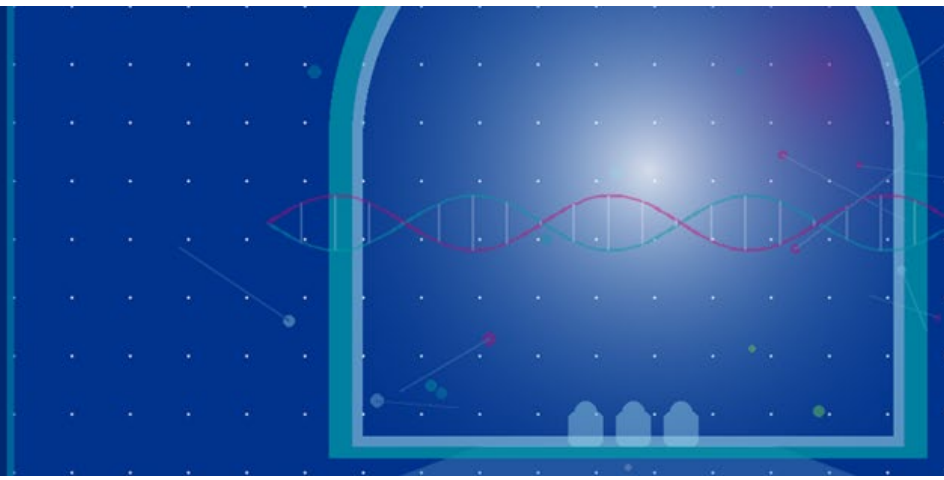


Genomic Insights into Pregnancy-Associated Anemia and Sickle Cell Disease

Qing Li, Staff Scientist, National Human Genome Research Institute
Mentor: Neil Hanchard
Authors: Qing Li;* Jacqueline Piekos; Neil Hanchard

Abstract: Alloimmunization, defined as the development of antibodies against non-self red blood cell (RBC) antigens following transfusion, is a major complication in individuals with sickle cell disease (SCD). Patients with SCD are particularly vulnerable due to lifelong transfusion exposure and antigenic disparities between predominantly African-ancestry recipients and a largely European-ancestry donor pool. This mismatch is especially consequential in highly polymorphic blood group systems. Genetic variation at the RH locus, including partial D variants, altered C/e antigens, and African-ancestry–specific RH haplotypes, substantially contributes to antibody formation even when conventional serologic matching appears adequate. In addition, interindividual variability in immune response—potentially influenced by HLA class II alleles, cytokine gene polymorphisms, and immune regulatory pathways—may further modify alloimmunization risk. Pregnancy-associated anemia in women with SCD represents another significant clinical challenge. Its etiology is multifactorial, reflecting baseline hemolysis, physiologic plasma volume expansion, iron homeostasis dynamics, inflammation, and nutritional factors. Genetic modifiers of SCD severity, including variants that influence hemolytic rate and fetal hemoglobin levels, may further modulate anemia severity during pregnancy and contribute to adverse maternal–fetal outcomes. Given their substantial impact on morbidity, transfusion complexity, and pregnancy outcomes, both alloimmunization and pregnancy-associated anemia warrant focused genetic investigation. To identify shared genetic susceptibility, we conducted a phenome-wide association study (PheWAS) within the All of Us Research Program, leveraging linked genomic and electronic health record data from an admixed population to detect variants jointly associated with RBC alloimmunization risk and pregnancy-associated anemia. Furthermore, we will interrogate associated genomic regions using long-read sequencing data to characterize structural variants that may underlie disease mechanisms and contribute to phenotypic heterogeneity.

Keywords: Sickle Cell Disease, Pregnancy, Anemia, Long Read Sequence Variant



HIV Proviral Populations Differ by Sex and Immune Activation Levels During Antiretroviral Therapy

Chuen-yen Lau, Staff Clinician, National Cancer Institute

Mentor: Frank Maldarelli

Authors: Chuen-yen Lau;* Thuy Nguyen; Matthew Adan; Jessica Earhart; Danielle Konlian; Lindsey Adams; Mary Zipparo; Robin Dewar; Jeanette Higgins; Catherine Rehm; Seble Kassaye; Anuradha Ganesan; Deborah Mcmahon; Robert J. Gorelick; Brian Luke; Frank Maldarelli

Background: Understanding mechanisms of persistence and expansion of HIV infected cells during antiretroviral therapy (ART) is critical to HIV control. Infected cells contain proviruses defective for replication, but express RNA and HIV proteins that contribute to pathogenesis. Roles of sex, age, and immune status in persistence are unclear. To investigate determinants of persistence and expression of HIV proviruses, we analyzed levels of total and gag-deleted proviruses and their RNA expression in the context of immunophenotypes in women and men with HIV (PWH) on long-term ART.

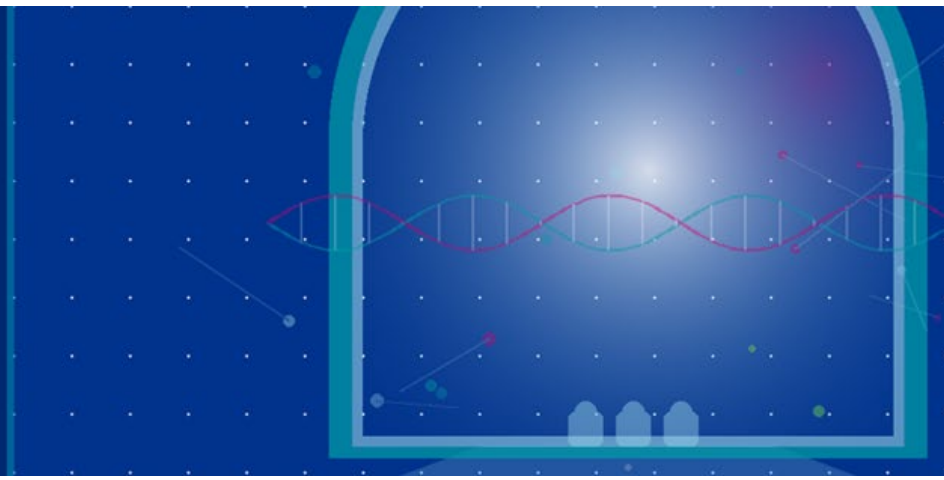
Hypothesis: Characteristics of HIV persistence differ between women and men.

Methods: Clinical information and peripheral blood mononuclear cells (PBMC) were obtained from PWH on ART with HIV RNA <50 c/ml for >3 years (y) in protocols at NIH, Walter Reed, and Women's Interagency HIV Study. Cell-associated HIV LTR and gag RNA and DNA were measured by multiplexed droplet digital PCR, and >20 lymphocyte subsets and activation markers by FACS. Clinical, immunologic, and virologic variables selected by univariable analysis were used to develop multivariable models for drivers of HIV DNA and RNA levels. Comparison of HIV persistence markers by sex and age <50y versus >50y was explored.

Results: Among 103 PWH, median age was 50y (range 27-80), 37% were women, median CD4 was 674 (250-1765) cells/μl, and median ART duration was 14.5y (3-31). Total HIV provirus levels did not differ by sex, but women had a higher proportion of gag-deleted proviruses (p=0.017). HIV gag expression (gag RNA/gag DNA) was >3-fold higher in women (p=0.0004). In men, age positively correlated with total proviruses, but negatively with total and gag RNA. CD16+CD56+ NK cells positively correlated with LTR and gag RNA per provirus. CD8Ro+ cell levels strongly correlated with proviruses in both sexes; other relationships were more complex. Differences in HIV parameters by sex were present only in the >50-year-olds (Mann-Whitney p<0.05 for gag DNA, LTR/gag DNA, LTR RNA/DNA and gag RNA/DNA).

Conclusions: Levels of HIV proviruses and CD8 memory cells correlate in all PWH; relative contributions of other immune and demographic characteristics to HIV persistence in women and men are complex. As markers of HIV persistence show correlations with age and sex, it is possible that hormone levels are influencing persistence dynamics. Sex and age are important considerations for HIV eradication and control strategies.

Keywords: HIV Persistence, Sex Differences, Immune Activation

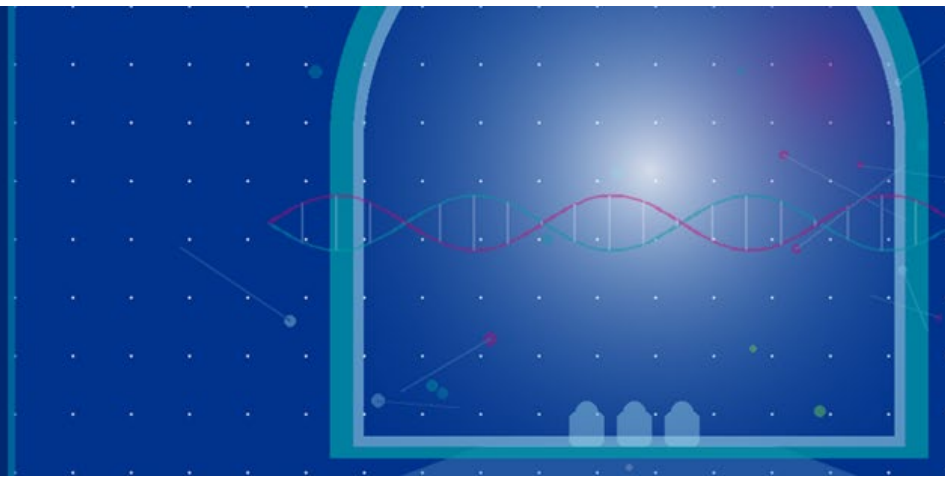


Kidney, Pregnancy, and Transcriptomics: An Unexplored Intersection

Jakub Jankowski, Visiting Fellow, National Institute of Diabetes and Digestive and Kidney Diseases
Mentor: Lothar Hennighausen
Authors: Jakub Jankowski;* Lothar Hennighausen

Background: Maternal morbidity and mortality rates are unacceptably high despite advancements in healthcare, and an increasing number of women entering pregnancy suffer from comorbidities like hypertension, chronic kidney disease or diabetes. Even in healthy pregnancy, the kidneys not only adjust to the new nutritional and hemodynamic needs of the body but are also subject to physical forces elicited by the growing uterus. Despite that, there is little known about genetic and epigenetic shifts governing those changes. Very few genomic datasets describing maternal renal health during pregnancy are publicly available, and none of them are human.
Aim: Our study aims to gather critically needed transcriptomic information about both the baseline and injured pregnant kidney with the goal of helping avoid common and preventable complications in the clinic.
Experimental design: As renal biopsies in pregnancy are exceedingly rare, we conducted the experiments in C56Bl/6 mice. We used bulk RNA-seq during pregnancy day 18 and lactation day 10 and compared it to baseline gene expression. We repeated our observations after using renal ischemia-reperfusion injury (IRI, 30' hypoxia, 24h reperfusion) to investigate changes in renal transcriptome during acute stress.
Results: We identified 823 significantly deregulated genes (DEGs) when comparing baseline to pregnancy, and 705 when compared to lactation, with a significant overlap of 272 genes, suggesting long-term changes persisting through lactation. Among the pathways affected by gestation-induced DEGs were hypoxia and Il2-STAT5 signaling, indicating ongoing stress response. Next, we performed bilateral IRI on days day 17 of pregnancy and day 9 of lactation to investigate the effects of renal injury. The pregnancies remained viable, and surprisingly there were no statistically significant differences in plasma creatinine, suggesting well-preserved kidney function. Bulk RNA-seq indicated gestational upregulation of hundreds of genes compared to control, including several known injury markers, such as Hmox1, Il-6, Cxcl1 and Ndrg1.
Conclusions: Our results show that pregnancy can on its own elicit significant and long-term changes in renal transcriptomics. While renal function might not be overtly affected by the subsequent acute injury, its effects on gene expression are extensive. We hope our results prompt further studies into gestation's effect on the kidney and aid in understanding kidney-associated complications.

Keywords: Pregnancy, Kidney Injury, Transcriptomics



LDL associates with decreasing NKp46 expression on NK cells in African American women, potentially contributing to the increased cardiovascular disease risk in African American women

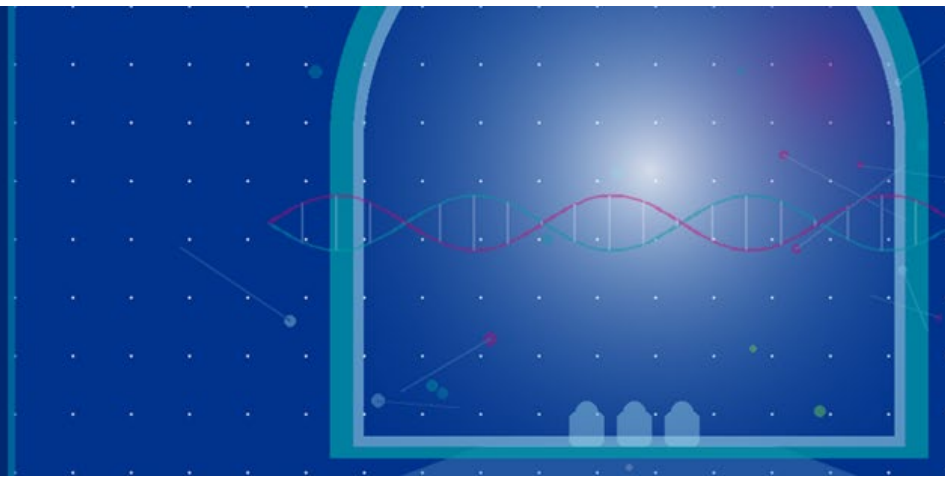
Yvonne Baumer, Staff Scientist, National Heart, Lung, and Blood Institute

Mentor: Tiffany Powell-Wiley

Authors: Yvonne Baumer;* Laurel Mendelsohn; Abhinav Saurabh; Elizabeth Aquino Peterson; Marcus Andrews; Shirley Lopez De Leon; Dana Sandler; Eleanor Seo; Marie Marah; Ayanna Wells; Sarah Deguzman; Azeb Redai; Valerie Mitchell; Joy Tolentino; Tiffany Powell-Wiley

Background: Dyslipidemia disproportionately affects African American (AA) women and contributes to disparate cardiovascular disease (CVD) outcomes. In a previous study, we showed that Natural killer cells are functionally impaired by hyperlipidemia, particularly LDL, in a DUSP1-dependent mechanism. However, the impact of dyslipidemia on NK cell activity-regulating receptor expression (e.g. NKp46), is still incompletely understood. Therefore, we sought to elucidate the potential impact of LDL on NK cell NKp46 expression in AA women.
Methods: NK cell-NKp46 expression was measured by flow cytometry in fresh blood samples of the Step It Up Physical Activity Intervention study participants (n=154). We used multivariable regression to examine associations between plasma lipid profile (LDL, HDL, triglycerides, and total cholesterol) and NK-NKp46 expression. Subsequently, we performed in vitro experiments with freshly isolated naïve NK cells +/- addition of LDL for overnight treatment. We used flow cytometry to determine a potential causal impact of LDL on NKp46 expression on NK cells.
Results: All Step It Up Physical Activity Intervention study participants were AA women (age 57, BMI 36.1, intermediate risk for CVD). In the unadjusted model, LDL associated negatively with NKp46 expression on all NK cells (⍰=-0.18, p=0.027), while no significant associations were found with HDL, triglycerides, or total cholesterol levels. These observed associations persisted after adjustment for BMI and ASCVD 10-year risk (⍰= -0.17, p=0.035). When focusing on the subsets of NK cells, LDL trended to significance with NKp46 on cytotoxic NK cells (p=0.077), while no associations were seen with NKp46 expression on proliferative NK cells (p=0.473). To determine if LDL could indeed cause a decrease in NK cell NKp46 expression levels, we treated isolated NK cells with LDL overnight. NKp46 expression on all NK cells was reduced by 6.78% (p=0.008), mainly driven by a 6.37% reduction on the cytotoxic NK cell subset (p<0.001), while the proliferative NK cell subset did not show any significant decrease in NKp46 expression levels (p=0.563).
Conclusion: Our data demonstrate that an LDL-induced reduction in NKp46 expression on NK cells could present an additional pathway by which hyperlipidemia impairs NK cell function, potentially accelerating CVD development and progression in AA women who are hyperlipidemia and CVD.

Keywords: Innate Immunity, NK Cells, LDL



Leptin Regulates Pathways Implicated in Pulmonary Arterial Hypertension and Sex-Dependently Modulates Pulmonary Vascular Tone

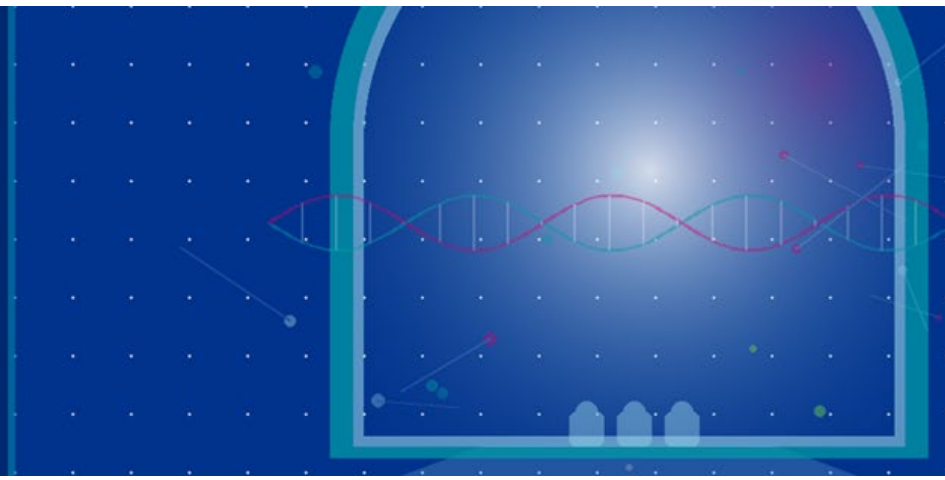
Daniels Konja, Visiting Fellow, Clinical Center

Mentor: Robert Danner

Authors: Daniels Konja;* Keytam Awad; Shuibang Wang; Colin Knight; Gabriela Ferreyra; Kadija Hersi; Jason Elinoff; Rebecca Brown; Robert Danner

Abstract: Background: PAH is a progressive, plexogenic arteriopathy of pre-capillary pulmonary arteries. BMPR2 mutations cause 70% of heritable PAH and women account for 70-80% of cases. Adiposity affects circulating leptin levels which in turn influence sex hormones, TGFs, BMPs and GDFs. Here, we investigated leptin effects on PAH-relevant pathways and mechanisms in human pulmonary artery endothelial cells (PAECs), patients, and isolated rat pulmonary arteries. Methods: PAECs were transfected with non-targeting siRNA or siBMPR2 for 48h, followed by incubation with vehicle or recombinant human leptin (10 ng/mL) for 24h; qPCR and Western blotting were performed for BMPR2, CAV1, leptin receptor (LEPR), and GDF15. Activin A, BMP9 and GDF15 were measured in cell supernatants by ELISA. Effects of leptin on pulmonary artery tone was assessed ex vivo in male and female Sprague-Dawley rats using myography. PAH-associated ligands and pathways were analyzed in 17 lipodystrophy patients with hypo-leptinemia treated with leptin for 12 days. Results: Human PAECs expressed LEPR, but not leptin. Leptin treatment upregulated BMPR2 and CAV1; and induced GDF15 in normal PAECs. Leptin suppressed vasoconstriction and augmented EC-derived nitric oxide vasodilation in male but not female rat pulmonary arteries. In patients with lipodystrophy, leptin significantly suppressed circulating PAH-relevant proteins associated with inflammation, oxidative stress, metabolic reprogramming, and vascular remodeling; and regulated BMP/TGFβ ligands. Conclusion: Leptin regulates ligands and pathways associated with the pathobiology of PAH supporting the notion that sex differences in leptin levels, obesity and metabolic syndrome affect PAH severity and progression. Direct sex-dependent effects of leptin on pulmonary artery tone may have implications for understanding, at least in part, sexual dimorphism in PAH.

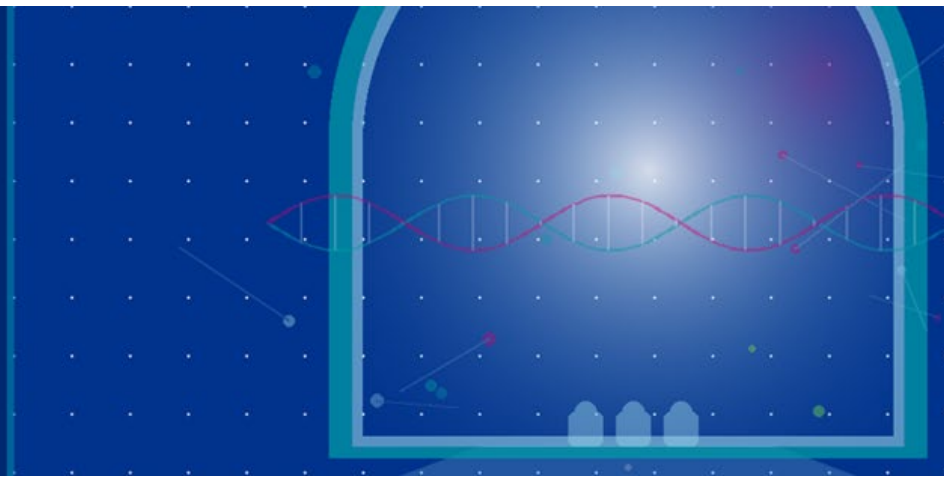
Keywords: Obesity, Leptin, Pulmonary Arterial Hypertension



Loneliness Modifies the Relationship Between Cortisol and Natural Killer Cell Function: A Potential Mechanism Connecting Psychosocial Stress to Impaired Immunity and Increased Cardiovascular Disease Risk

Abhinav Saurabh, Visiting Fellow, National Heart, Lung, and Blood Institute
Mentor: Tiffany Powell-Wiley
Authors: Abhinav Saurabh;* Yvonne Baumer; Laurel Mendelsohn; Elizabeth M. Aquino Peterson; Marcus Andrews; Shirley Lopez De Leon; Dana Sandler, Jein Seo, Marie Marah, Ayanna Wells, Sarah Deguzman, Azeb Redai, Valerie Mitchell, Katherine Joy Tolentino, Powell-Wiley

Background: Chronic stress accelerates cardiovascular disease (CVD), disproportionately affecting African American (AA) women in under-resourced neighborhoods. However, potential connections between psychosocial stressors, cortisol, and Natural Killer cells are largely understudied.
Methods: 186 AA women were recruited in the Step It Up Physical Activity Intervention. In baseline blood samples, NK cells and subsets were measured by flow cytometry. Fasting plasma cortisol levels at 8-9 am were measured by ELISA. Psychosocial stressors (depression, chronic stress, social isolation, and loneliness) were determined using validated questionnaires. Associations between cortisol and NK cell distribution were examined with multivariable linear regression; psychosocial factors were tested as effect modifiers of the relationships. All models were adjusted for age, SES, and CV risk factors, daily step count, diet, and inflammatory comorbidities. In vitro NK cell receptor-mediated degranulation and cytokine production were measured in the presence or absence of cortisol (300 nmol/L), using flow cytometry after exposure to the K562 target cell line.
Results: Step It Up study participants were AA women (mean age 57 +/- 12 years, mean BMI 36.3 +/- 7 kg/m^2, at intermediate CVD risk). Cortisol was negatively associated with the proportion of proliferative NK cells (β=-0.21, p= 0.006. Among the psychosocial measures, loneliness and chronic stress were negatively associated with overall NK cell proportions (β= -0.16, p= 0.04 and β= -0.17, p= 0.02, respectively). Loneliness modified the cortisol-proliferative NK cell association, where cortisol negatively associated with proliferative NK cells among those with higher loneliness (β= -0.3, p=0.04; p= 0.01 for cortisol*loneliness interaction). Further testing the hypothesis that cortisol impacts NK cell function, we found that 24-hour in vitro cortisol exposure reduced NK cell degranulation under baseline and activating conditions (8.4% vs 4.9% and 42.4% vs 37.6% CD107a+NK cells). In contrast, intracellular IFN-γ and TNF-α expression were significantly reduced only under activating conditions, when compared to untreated controls.
Conclusion: Increasing cortisol levels, especially in individuals with higher self-reported loneliness, may reduce NK cell number and function, leading to impaired NK cell-mediated immunity. This suggests a psychosocial–neuroendocrine–immune pathway that could contribute to increased cardiometabolic disease risk.
Keywords: Loneliness, Women, Obesity, Population Science

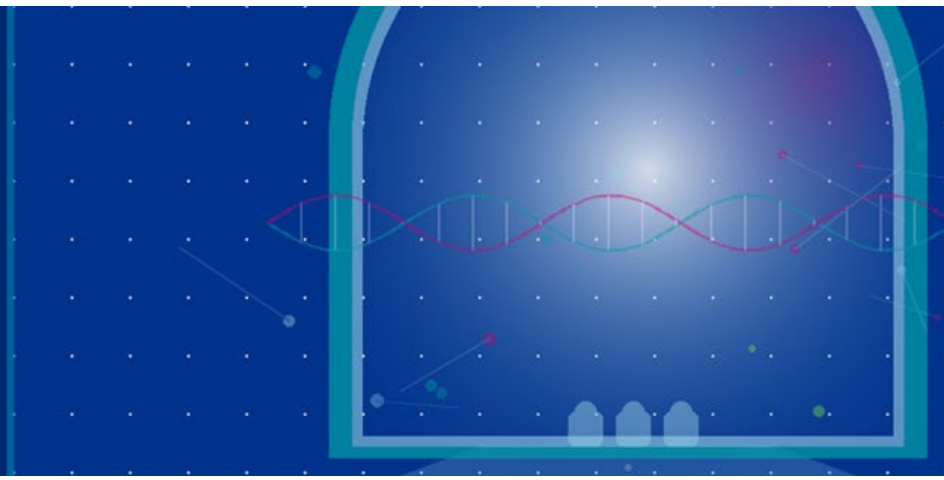


Microplastics in damaged tissue induce autoimmune tertiary lymphoid structure formation constrained by CD8+ Ly49+ T cells

Aditya Josyula, Visiting Fellow, National Institute of Biomedical Imaging and Bioengineering
Mentor: Kaitlyn Sadtler
Authors: Aditya Josyula;* Daphna Fertil; Mayowa Amosu; Isabella Horton; Devon Hartigan; Kaitlyn Sadtler

Abstract: Tissue damage, whether accidental, surgically induced or secondary to infection can trigger autoimmunity. Microplastics arising from environmental exposure and biomedical implants accumulate in damaged tissue. Here, we investigated whether such microplastics could potentiate autoimmunity in the context of tissue damage using a mouse model of volumetric muscle loss and reconstruction (wherein mice receive an untreated control injury, pro-inflammatory microparticulate polyethylene (150 um diameter) or pro-regenerative decellularized extracellular matrix (ECM) treatment). We found that skeletal muscle injury induced ectopic germinal center (GC) formation. In addition to draining lymph nodes, these local germinal centers gave rise to antibody secreting plasma cells. We observed that plasma cell formation in local GCs was significantly higher with microplastics in tissue as compared to both control injury and mice receiving ECM treatment. Further, both control injury and ECM treatment led to significantly higher circulating IgE as compared to pre-injury levels. Using single cell RNA sequencing data from injured muscle and draining lymph node, we found that IgA producing plasma cells arise from the lymph nodes as early as 1 week post injury across treatment groups. However, only microplastics induced IgA producing plasma cells within muscle tissue. Across treatment groups, Cd8a depletion led to significantly increased serum levels of the T-dependent antibody isotypes IgG1, IgG2a, IgG2b, and IgE compared to pre-injury levels. This elevation was fully mirrored by Batf3-/- mice which lack conventional dendritic cells type 1 (cDC1s) suggesting that cross-presentation of antigens to CD8+ T cells partly arbitrates isotype switching after tissue damage. Additionally, we compared plasma cell generation in ectopic germinal centers in NOD WT and NOD Aire -/- mice. While Aire deletion did not affect plasma cell numbers in control injury and ECM treatment groups, microplastics synergized with lack of central tolerance to increase local plasma cell generation by approximately 10-fold. Lastly, we observed that cDC1s spatially colocalize in-vivo and preferentially stimulate Ly49 (A-C-I-F-H) expressing CD8+ T cells in-vitro. Both cell types were enriched in the muscle by ECM treatment and depleted by microplastics which corroborated their crosstalk. Cumulatively, our data supports the hypothesis that Ly49+ CD8+ T cells govern ectopic germinal centers induced by tissue damage.

Keywords: Tertiary Lymphoid Structures, Autoantibodies, CD8 T Cells

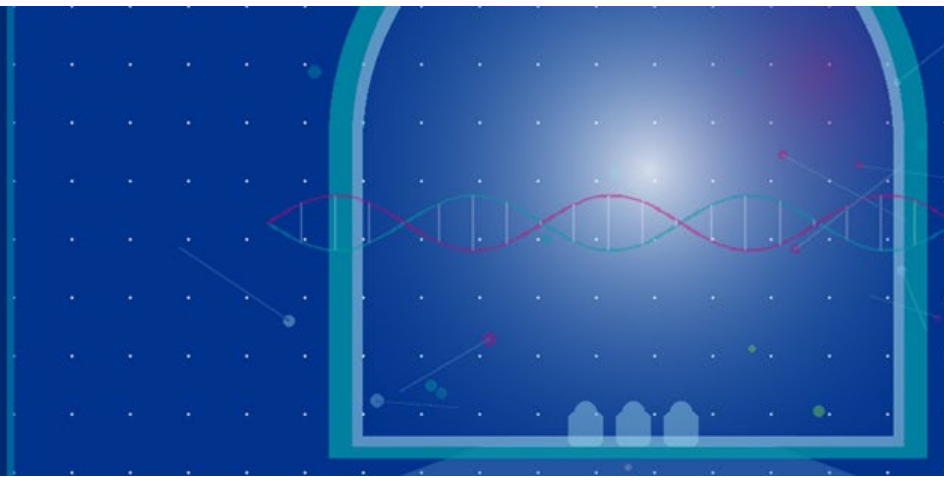


MYBBP1A Is Part of a Mechanically Modulated System That Alters Breast Cancer Metastatic Potential by Regulating Focal Adhesion

Xi Chen, Visiting Fellow, National Cancer Institute
Mentor: Kent Hunter
Authors: Xi Chen;* Kent W. Hunter

Abstract: MYB binding protein 1a (MYBBP1A) was first identified for its ability to bind and repress the proto-oncogene c-MYB. Most research focuses on its role in regulating ribosomal RNA (rRNA) transcription; However, its impact on metastasis remains unclear. Analysis of TCGA breast cancer patient data reveals higher MYBBP1A levels are associated with shorter survival times in breast cancer patients, while a Mybbp1a knockdown (KD) gene signature, generated by machine learning, indicates significantly improved patient survival outcomes. Using mouse spontaneous metastasis model, we confirmed that MYBBP1A loss suppresses breast cancer cell metastasis. Further analysis revealed that Mybbp1a KD cells exhibit robust abnormalities in cell morphology, which is associated with disrupted F-actin organization. And that are partially rescued in high stiffness extracellular matrix (ECM) culture, indicating MYBBP1A could be part of a mechanically modulated system that alters breast cancer metastatic potential. This is supported by the observation that MYBBP1A levels exhibit a gradually increase in response to the increases of ECM stiffness. Mechanical stimuli from the tumor microenvironment play an important role in mediating breast cancer metastasis. The pathways that cancer cells use to sense and leverage mechanical cues are largely driven by the assembly and disassembly of focal adhesions, which regulate the dynamics of F-actin stress fibers and couple F-actin with the extracellular matrix (ECM) to transduce mechano-signaling to nucleus and regulate cell motility. Our data shows focal adhesion is reduced in Mybbp1a KD cells, evidenced by weakened level and number of phospho-FAK clustering at the points of F-actin. In parallel, overexpression of FAK rescues breast cancer cell phenotypes and partially restores the reduced cell metastasis capacity observed in Mybbp1a KD. In exploring the function of MYBBP1A in regulating mechanosignal transduction, we found that SUN2, an important component of the Linker of Nucleoskeleton to the Cytoskeleton (LINC) complex, was stripped from nuclear envelop and relocated to heterochromatin dense area, upon Mybbp1a KD. That breaks the connection between nucleus and cytoskeleton and could explain the reduced focal adhesion assembly following Mybbp1a KD. In the future, we will keep studying the role of MYBBP1A as part of a mechanically modulated complex that is important in promoting breast cancer metastasis.

Keywords: Metastasis, Focal Adhesion, Mechanosensing

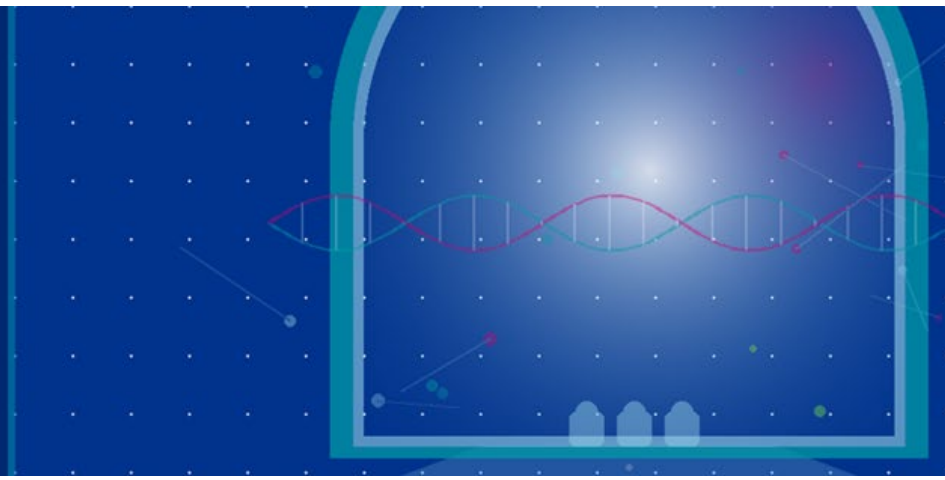


Nanobody-based Bioconjugates for Targeted HIV Inhibition

Shubhra Saha, Visiting Fellow, National Institute of Diabetes and Digestive and Kidney Diseases
Mentor: Ross Cheloha
Authors: Shubhra Saha,* Ross Cheloha

Abstract: Human immunodeficiency virus (HIV) and causes immune depletion, leading to AIDS and death if untreated. There is currently no cure or vaccine to prevent HIV infection, necessitating the development of new therapeutic approaches. Envelope glycoprotein found on the HIV surface binds to the immune cell surface proteins (CD4, CXCR4, CCR5) to facilitate fusion between viral and host membranes, resulting in viral infection. Anti-HIV fusion inhibitor peptides (FIs) have been developed to block this process and treat infection; however, these approaches suffer from drawbacks such as toxicity and the emergence of drug resistance. Here, we describe a new approach for the localized delivery of antiviral FIs that relies on the binding of antibody fragments known as nanobodies (Nbs). We link synthetic peptides that act as FIs to Nbs to generate novel, chimeric antiviral conjugates. Such conjugates are generated using a combination of synthetic peptide chemistry, recombinant antibody expression, and enzymatic conjugation chemistry. These conjugates enable delivery of FIs to cells susceptible to HIV infection by using Nbs specific for cell surface markers (CD4 and CXCR4) expressed in this context. We confirmed that Nbs maintain binding to specified cell surface proteins using flow cytometry. We assessed the efficacy of Nb-FI peptide conjugates using a cell-based HIV pseudovirus neutralization assay. Cells engineered to express CD4 and CCR5 were exposed to HIV pseudovirus (Yu-2 strain) expressing HIV fusion machinery. These experiments showed that Nb-FI conjugates outperformed FI peptides alone, with improvements in potency of nearly 1000-fold. We hypothesize that the use of a delivery vector Nb will ensure routing of FIs to the surface of cells susceptible to viral infection. Such a delivery mechanism may allow for the use of lower doses of antiviral compounds with a concomitant reduction in side effects, a common problem with anti-HIV peptide therapeutics. Beyond simply serving as a delivery mechanism, Nbs that target surface receptors such as CD4 and CXCR4 can themselves contribute to antiviral activity. The ability to engage multiple mechanisms of antiviral activity (blockage of receptor binding, inhibition of viral protein conformational changes) provides a route towards raising the barrier to viral resistance mechanisms, a longstanding goal of HIV therapeutic development. These hypotheses will be tested using HIV strain libraries and in vivo experimentation.

Keywords: Nanobody, Bioconjugate, Peptide

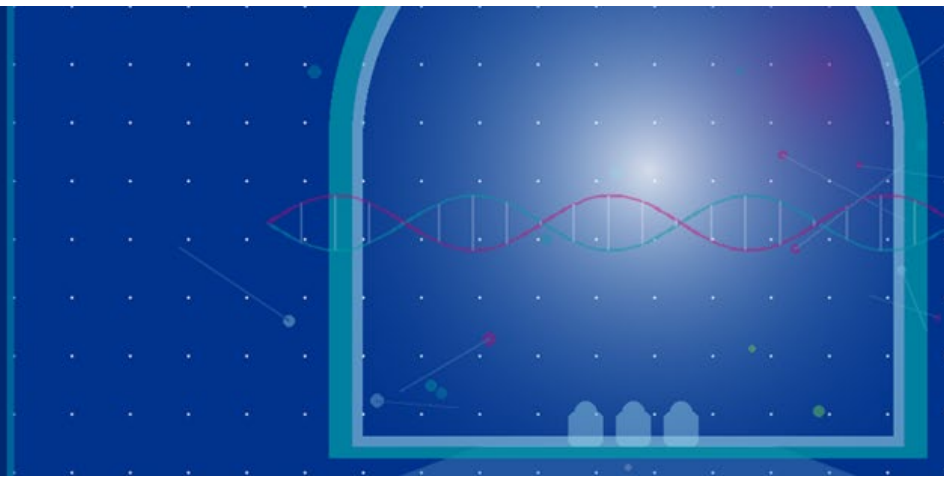


Nutrition and Physical Activity Guidance for GDM Management Among Latina Women: Disparities, Challenges, and Food as Medicine Solutions

Juliana Camargo, IRTA Postdoc, National Institute on Minority Health and Health Disparities
Mentor: Kelvin Choi
Authors: Juliana Camargo;* Gabriela Recinos; Amanda Hinerman; Eliseo Perez-Stable; Kelvin Choi

Scientific Background: Although 70-85% of women with gestational diabetes (GDM) achieve glucose control through diet and physical activity, Latina women show significantly lower rates (~60%) and greater insulin dependence.
Research Questions: What are the perspectives of Latina women with GDM on the challenges and facilitators of dietary and physical activity guidance for blood glucose management?
Methodology: Semi-structured interviews and a sociodemographic survey were conducted in 2025 with 40 Latina women who self-reported a GDM diagnosis (current on within the previous 5 years), completed online or by phone, recorded and transcribed verbatim. Participants were recruited through community events, a GDM clinic, and social media. We explored their dietary management experiences during pregnancy. Sociodemographic characteristics were analyzed descriptively; qualitative data used thematic analysis grounded in the Nutrition Health Disparities and Social Cognitive Theory frameworks.
Results: Most received dietary guidance focused on carbohydrate restriction and portion control, with limited direction on food alternatives. Glucose monitors were commonly used to identify lower glycemic foods. Regarding physical activity (PA), participants reported that PA guidance was often absent from GDM care, and when provided, recommendations were broad and lacked specificity in how to exercise. Participants expressed a desire for actionable guidance on both what to eat and how to be physically active. Food Is Medicine approaches, such as tailored groceries and meals, were identified as potentially helpful interventions.
Conclusions: Family history of diabetes and food insecurity were common among Latina women with GDM, suggesting elevated type 2 diabetes risk. Nutrition counseling focused on positive food choices, physical activity counseling focused on physical activity literacy for pregnancy and Food Is Medicine strategies may represent promising intervention targets for this population.

Keywords: Chronic Disease Management, Physical Activity, Nutrition Therapy

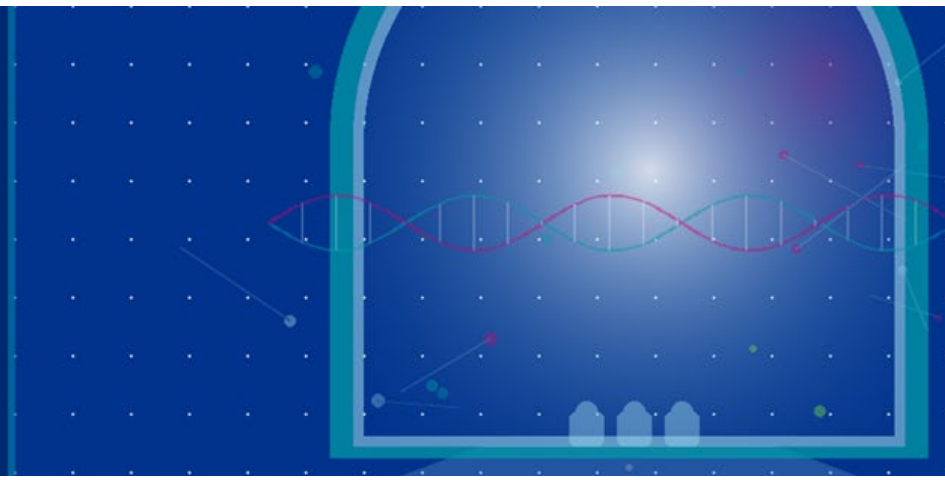


Oral Antigens Ingested During a Viral Respiratory Infection Elicit Aberrant Immune Responses and May Lead to Food Allergy

Kathryn Laporte, IRTA Postdoc, National Institute of Allergy and Infectious Diseases
Mentor: Andre Ballesteros-tato
Authors: Kathryn M. Laporte,* Holly Bachus, Shivangi Dave, Andre Ballesteros-tato

Abstract: Oral tolerance maintains immune hyporesponsiveness to food. In the mesenteric (gut-draining; mes) lymph nodes (LNs), CD4+ T cells induce oral tolerance by differentiating into regulatory T cells, becoming anergic, or dying. Disruption of these mechanisms can lead to food allergies, which can elicit particularly severe side effects in adult women. While the mes LN is the primary site for food antigen sampling, studies suggest that food antigens can also enter the bloodstream. Whether circulating food-allergen-derived antigens reach non-gut-draining LNs and influence food tolerance remains unclear. Here, we show that oral administration of ovalbumin (OVA) results in rapid systemic dissemination of OVA, as observed in the blood. In addition to the mes LN, OVA-specific CD4+ T cell responses are also primed in the lung-draining mediastinal (med) LN. OVA-specific CD4+ T cells in both the med LN and mes LN both become tolerized, however, when OVA is ingested following infection with a mouse-adapted influenza A strain (PR8), the number of OVA-specific CD4+ T cells increases in the med LN of PR8-infected OVA-fed mice compared to uninfected controls, while responses in the mes LN remain unchanged. This correlates with the presence of IgE+ OVA-specific plasma cells in PR8-infected OVA-fed mice but not in controls. These findings suggest that the induction of food-specific IgE in gut distal LNs during inflammation may represent a mechanism for breaking oral tolerance. Understanding the mechanisms behind aberrant immune responses to food antigens in inflammatory environments and distal LNs is important for developing strategies to prevent food allergies.

Keywords: Immunology, Allergy, Viral Infection



p53-induced RNA-binding protein ZMAT3 inhibits transcription of a hexokinase to suppress mitochondrial respiration

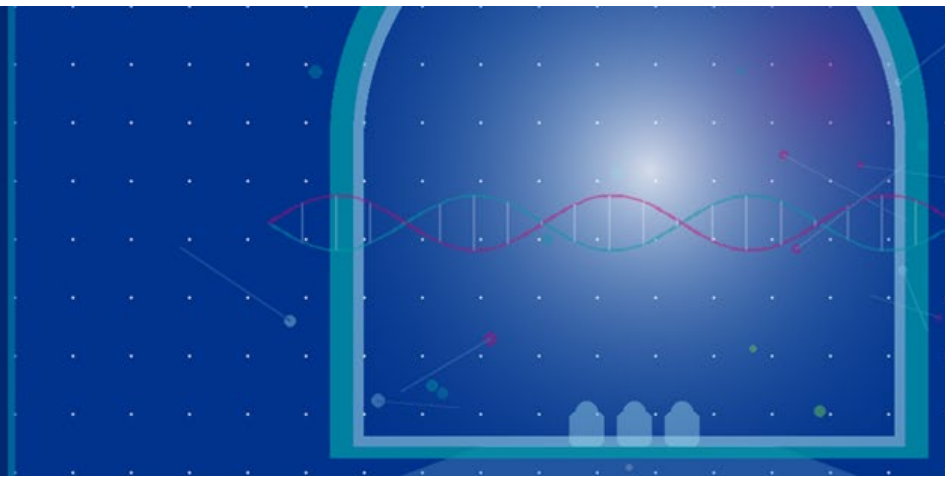
Ravi Kumar, Visiting Fellow, National Cancer Institute

Mentor: Ashish Lal

Authors: Ravi Kumar;* Simon Couly; Bruna R. Muys; Xiao Ling Li; Ioannis Grammatikakis; Ragini Singh; Mary Guest; Xinyu Wen; Wei Tang; Stefan Ambs; Lisa M. Jenkins; Erica C. Pehrsson; Raj Chari; Tsung-ping Su & Ashish Lal

Abstract: The tumor suppressor p53 is a transcription factor that controls the expression of hundreds of genes. Emerging evidence indicates that the p53-induced RNA-binding protein ZMAT3 acts as a key splicing regulator that contributes to p53-dependent tumor suppression in vitro and in vivo. However, the mechanism by which ZMAT3 functions within the p53 pathway remains largely unclear. Here, we discovered a function of ZMAT3 in inhibiting transcription of HKDC1, a hexokinase that regulates glucose metabolism and mitochondrial respiration. Quantitative proteomics revealed HKDC1 as the most significantly upregulated protein in ZMAT3-depleted colorectal cancer cells. ZMAT3 depletion resulted in increased mitochondrial respiration, which was rescued by simultaneous depletion of HKDC1, suggesting that HKDC1 is a critical downstream effector of ZMAT3. Unexpectedly, ZMAT3 did not bind to HKDC1 RNA or DNA; however, proteomic analysis of the ZMAT3 interactome identified its interaction with the oncogenic transcription factor JUN. ZMAT3 depletion enhanced JUN binding to the HKDC1 locus, leading to increased HKDC1 transcription that was rescued upon JUN depletion, suggesting that JUN activates HKDC1 transcription in ZMAT3-depleted cells. Collectively, these findings uncover a mechanism by which ZMAT3 regulates transcription through JUN and demonstrate that HKDC1 is a key component of the ZMAT3-regulated transcriptome in the context of mitochondrial respiration regulation.

Keywords: p53, ZMAT3, RNA-binding protein, Cancer



Poziotinib, a brain-penetrant ErbB inhibitor, targets HER2-positive breast cancer brain metastasis

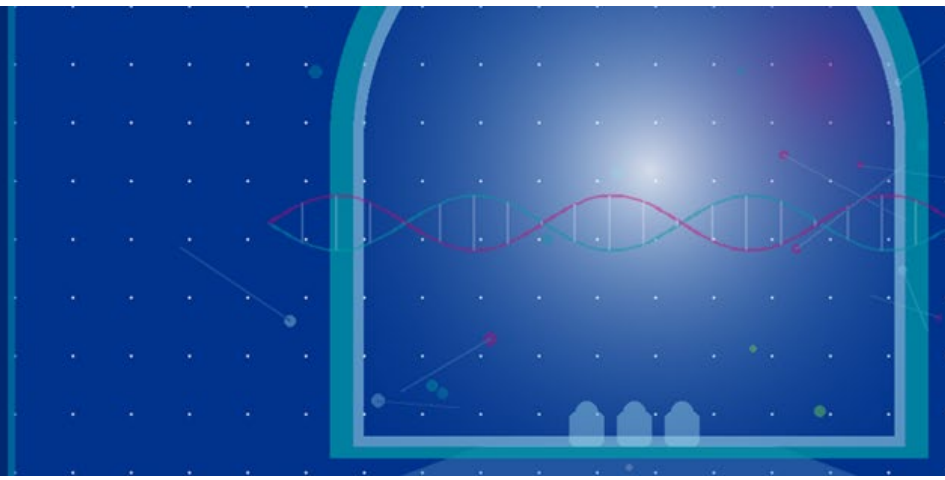
Yi-han Lin, Contract Scientist, National Center for Advancing Translational Sciences

Mentor: Mark Henderson

Authors: Yi-han Lin;* Danyyl Ippolitov; Raul Calvo; Darian Williams; Abhijeet Kapoor; Amy Wang; Xin Xu; Thomas Klonisch; Sabine Hombach-klonisch; Juan Marugan; Mark Henderson

Abstract: Breast-to-brain metastasis occurs most frequently in patients with aggressive subtypes, particularly HER2-positive breast cancer. Many chemotherapeutic agents effective against HER2-positive breast tumors are not suitable for brain metastases due to poor penetration through the blood–brain barrier, underscoring the urgent need for central nervous system (CNS)-penetrant therapeutics. We developed a novel patient-derived luminal B HER2-positive breast-to-brain metastasis model, BCBM94, which consistently generated brain metastasis in mice by hematogenic xenografting. Using this model, we optimized a high-throughput screening assay and evaluated more than 8,000 compounds consisting of investigational oncology agents, pharmacologically active chemicals, and approved drugs, using the CellTiter-Glo viability assay. A human mammary epithelial cell line (HME1) was used as a counterscreen to exclude non-selective cytotoxic agents. Among the BCBM94-selective compounds, the most enriched targets were within the ErbB receptor tyrosine kinase family. We subsequently evaluated a panel of 50 ErbB inhibitors differing in mechanism of action, receptor selectivity, and predicted CNS penetration, in the BCBM94 model. Poziotinib, a covalent pan-ErbB inhibitor, demonstrated the greatest activity, with an AC50 of approximately 6 nM. It was also active in another luminal B HER2-positive cell line, BT474, with comparable potency, while no activity was observed in the triple-negative breast cancer MDA-MB-231. Notably, the neuregulin-1–dependent resistance mechanism that reduces the efficacy of lapatinib, a clinically used ErbB2 inhibitor, was not observed with poziotinib. Combining poziotinib with additional pharmacological agents, including Brd4 and HDAC inhibitors, showed synergistic effect in eliminating BCBM94 and BT474 in vitro. Pharmacokinetic studies in mice demonstrated that brain concentrations of poziotinib remained well above the in vitro EC50 for 24 hours following a single 4 mg/kg subcutaneous dose. Finally, in vivo treatment of poziotinib successfully ablated BCBM94 and BT474 tumors in two weeks.

Keywords: HER2-positive breast cancer, Breast-to-brain metastasis

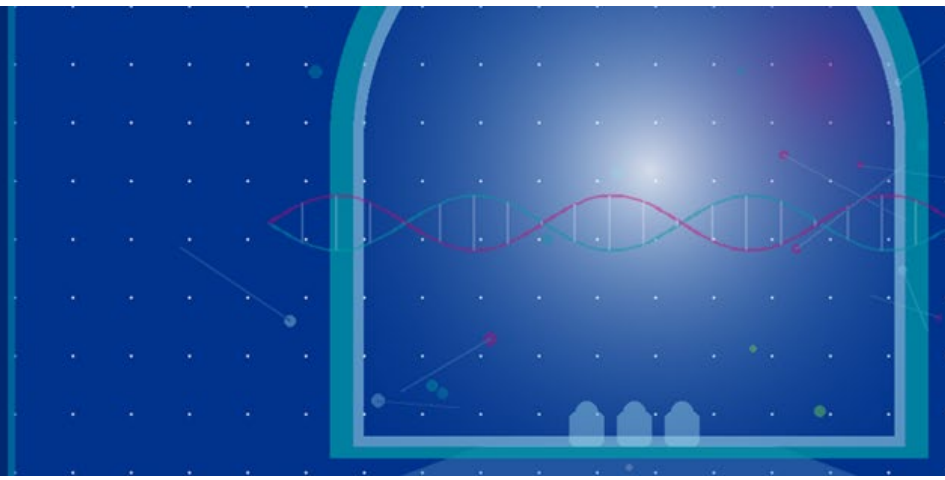


Pre-pregnancy Anxiety and Depression as Predictors of Obstetric Complications in Women: An Analysis of The *All of Us* Research Program National Database

Aminata Sinyan, External Mentee Under Excellence in Mentorship for Unity, Resilience, and Growth(EMURG) Mentorship Program at Johns Hopkins, Clinical Center
Mentor: Jennifer Barb
Author: Aminata J. Sinyan

Main Question: To what extent does pre-pregnancy diagnosis of anxiety or depression increase the risk of obstetric complications – postpartum hemorrhage, intrapartum hemorrhage, postpartum embolism, and cerebrovascular stroke – among women within the United States? **Secondary Question:** How is the relationship mediated by social determinants?
Introduction: Maternal health outcomes in the United States (US) are increasingly recognized as an accumulation of biopsychosocial stressors. Maternal depression occurs in 8.3% to 12.7% of pregnant women in the US. Studies documented the association between pre-pregnancy depression and the risk of preterm births; however, the role of pre-existing mental health diagnoses remains a critical research gap. This study investigates the association between pre-pregnancy anxiety and depression and complications in obstetric outcomes in the US.
Methods: The NIH-funded All of Us Research Program database, using the methods of Smith et al. (2024, included 18,970 pregnancy episodes. The pre-pregnancy diagnoses of anxiety and depression were the independent variables, and the primary outcomes were obstetric complications, including postpartum hemorrhage, intrapartum hemorrhage, postpartum embolism, and cerebrovascular events. Chi-square analyses were used to examine the association between mental health diagnoses and obstetric complications. Future analyses will include multivariate logistic regression to estimate risk-adjusted odds ratios, controlling for sociodemographic variables and co-morbid conditions.
Results: Chi-squared analysis yielded a significant association between pre-pregnancy depression and an increase in obstetric complications ($\chi^2 = 21.25$, $p < 0.001$, $df = 1$). Chi-squared analysis yielded a statistical association between pre-pregnancy anxiety and increased postpartum complications ($\chi^2 = 14.29$, $p = 0.001$, $df = 1$).
Conclusion: This preliminary analysis suggests that individuals with a history of pre-pregnancy depression and anxiety may face higher obstetric complications. Integration of mental health screening and social supports may improve perinatal outcomes. Further study is warranted to examine the associations among co-occurring medical conditions, sociodemographic factors, and pregnancy complications.

Keywords: Maternal Mental Health, Obstetric Complications, *All of Us* Research Program



PROX1 Increases Vascular Permeability and Causes Blood-brain Barrier Breakdown in Neurovascular Diseases

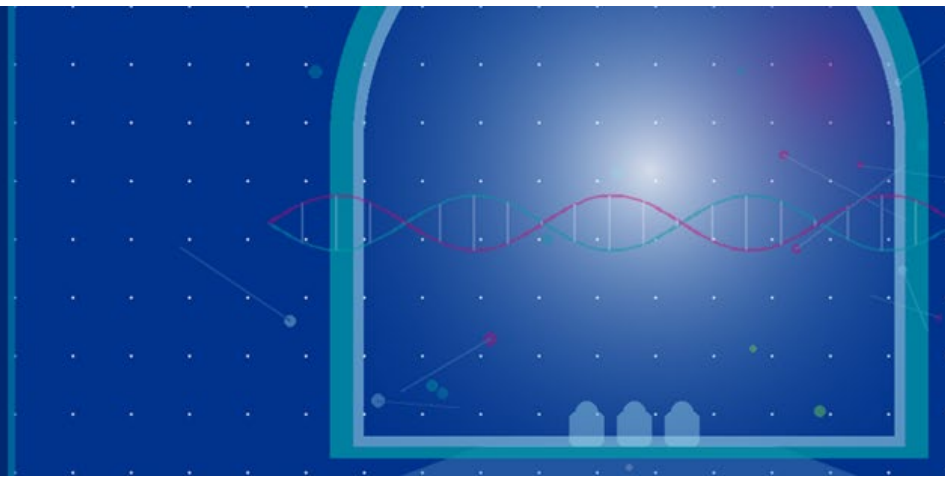
Sara Gonzalez Hernandez, IRTA Postdoc, National Heart, Lung, and Blood Institute

Mentor: Yosuke Mukoyama

Authors: Sara Gonzalez-Hernandez;* Ryo Sato; Yuya Sato; Chang Liu; Wenling Li; Chengyu Liu; Zulfeqhar a Syed; Sadhana Jackson; Yoshiaki Kubota; Yoh-suke Mukouyama

Abstract: The blood-brain barrier (BBB) regulates CNS homeostasis by regulating vascular permeability and controlling immune cell entry. BBB dysfunction is a hallmark of neurovascular diseases, such as glioblastoma, brain arteriovenous malformations (bAVMs), and brain metastases. PROX1, a key transcription factor for lymphatic differentiation, is normally absent in CNS endothelial cells (ECs); however, our analysis of publicly available single-cell RNA sequencing datasets from patients with glioblastoma, bAVMs, and brain metastases revealed that PROX1, along with the vascular permeability marker PLVAP, is aberrantly expressed in ECs across all these conditions. These findings suggest that PROX1 may contribute to vascular abnormalities and BBB disruption. To address this further, we generated a mouse model with inducible Prox1 overexpression in ECs. Using both pan-EC (Cdh5-CreERT2) and brain-EC (Slco1c1-CreERT2) drivers, we induced Prox1 expression after the BBB maturation. This led to vascular malformations, increased permeability, and BBB disruption when induced postnatally or adult stages, demonstrating that Prox1-mediated vascular defects occur independently of the timing of development. Mechanistically, PROX1 directly represses the expression of Claudin-5 and β-catenin, which are key regulators of BBB integrity, resulting in impaired tight junctions and increased transcytosis. Overall, our findings establish Prox1 as a significant driver of BBB dysfunction in neurovascular diseases. We are currently focusing on managing endothelial Prox1 expression in mouse models of glioblastoma to test whether this intervention can restore BBB integrity and improve treatment outcomes for glioblastoma.

Keywords: PROX1, Blood-brain Barrier, Neurovascular Diseases

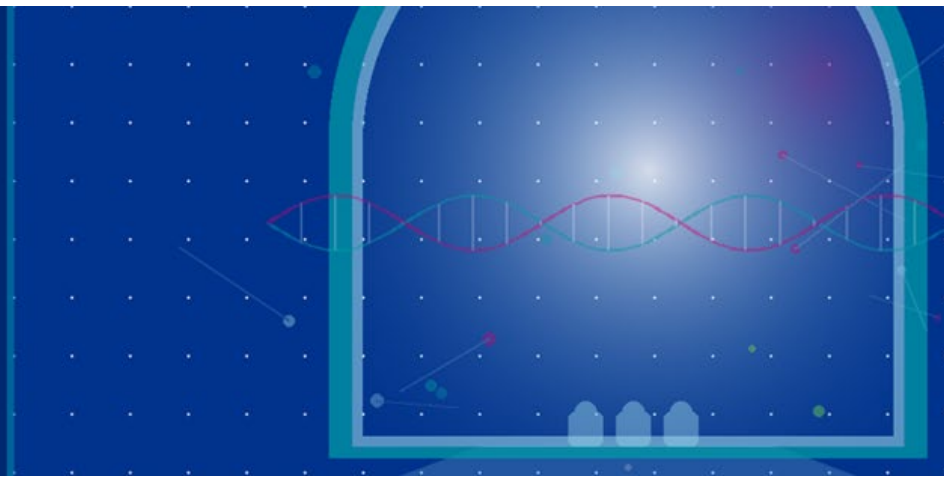


Reasoning Over Heterogeneous Graphs for Medical Cross-modal Retrieval

Zhaohui Liang, Visiting Fellow, National Library of Medicine
Mentor: Sameer Antani
Authors: Zhaohui Liang,* Niccolo Marini, Sivaramakrishnan Rajaraman, Zhiyun Xue, Sameer Antani

Scientific background: Cross-modal retrieval of medical radiographs is widely used for clinical decision support, cohort discovery, and large-scale data reuse. Vision–language models such as CLIP enable zero-shot retrieval by aligning images and reports in a shared embedding space. However, ranking retrieval based only on embedding similarity does not explicitly capture higher-order relationships among images, reports, and clinical semantics, which can limit retrieval quality and robustness.
Hypothesis: We hypothesize that explicitly modeling structured relationships among radiographs and reports through heterogeneous graph reasoning can improve medical cross-modal retrieval performance without retraining or modifying the underlying vision–language model.
Methodology: We propose CLIP-HGNN, a graph-based re-ranking framework that operates on top of an initial CLIP retrieval. The method constructs a heterogeneous k-nearest-neighbor graph over image and report embeddings and applies relation-aware message passing across modality-specific and clinically grounded node types to refine candidate rankings. We instantiate the method using representative graph neural network architectures, including neighborhood aggregation, spectral propagation, and attention-based weighting.
Results: We evaluate CLIP-HGNN on chest radiograph retrieval using two large public datasets under both within-dataset validation and cross-dataset transfer. Heterogeneous graph re-ranking consistently improves retrieval quality across settings, with the largest gains observed for text-to-image retrieval and clinically meaningful multi-label matching. On smaller datasets, graph-based reasoning substantially strengthens ranking accuracy, while on larger datasets it provides more moderate but consistent improvements. Performance gains remain stable under dataset shift, indicating improved robustness compared with similarity-based retrieval alone.
Conclusions and implications: These findings show that heterogeneous graph reasoning offers a practical and effective extension to CLIP-based medical retrieval systems, improving ranking quality and generalization without altering foundation models. The proposed method provides a scalable approach for enhancing cross-modal retrieval in large medical imaging repositories where accurate alignment between visual and textual clinical information is critical.

Keywords: Cross-modal Retrieval, Graph Neural Networks, Medical Image Retrieval

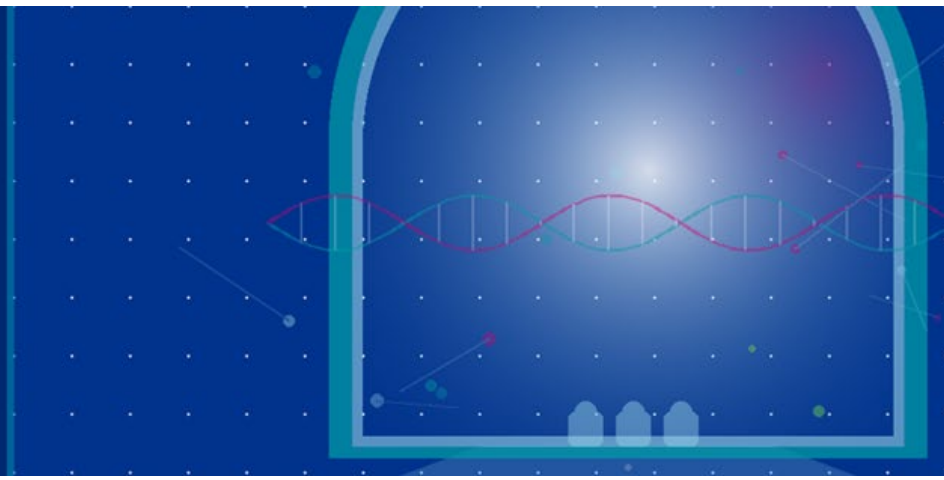


Regulatory Risk Loci Link Disrupted Androgen Response to Pathophysiology of Polycystic Ovary Syndrome

Jaya Srivastava, Visiting Fellow, National Library of Medicine
Mentor: Ivan Ovcharenko
Authors: Jaya Srivastava* and Ivan Ovcharenko

Abstract: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder with heterogeneous reproductive and metabolic manifestations, yet a critical gap remains between its widespread symptoms and limited understanding of the underlying genetic and molecular mechanisms. This gap has constrained the development of targeted therapies. Genome-wide association studies have identified numerous non-coding PCOS susceptibility variants, making it challenging to elucidate their functional roles. This highlights the need to investigate regulatory pathways perturbed across diverse cell-types that collectively contribute to pathophysiology. We integrated molecular and epigenomic annotations across pathogenic cell types and applied a deep learning model to infer cell-type-specific regulatory effects of risk variants across susceptibility loci. Our analysis revealed that these variants affect key transcription factor (TF) binding sites, including NR4A1/2, NHLH2, FOXA1, and WT1, which regulate gonadotropin signaling, folliculogenesis, and steroidogenesis across brain and endocrine cell types. The model showed strong concordance with reporter assay data and identified enhancer-disrupting activity in 20% of risk variants. Many of these disrupt TFs mediate androgen signaling, providing molecular insights into hyperandrogenemia in PCOS. Using the IRX3-FTO locus, we demonstrate how regulatory disruptions in fetal brain, pancreas, adipocytes, and endothelial cells may link obesity-associated mechanisms to PCOS pathogenesis via neuronal development, metabolic dysfunction, and impaired folliculogenesis. Collectively, our findings highlight the utility of our approach to uncover disease-relevant variants, reveal cross-tissue regulatory effects, and refine mechanistic understanding of PCOS. Experimental characterization of these variants has the potential to pave the way for novel, symptom-targeted therapies for PCOS patients and advance women's health research.

Keywords: Polycystic Ovary Syndrome, Regulatory Genomics, Deep Learning

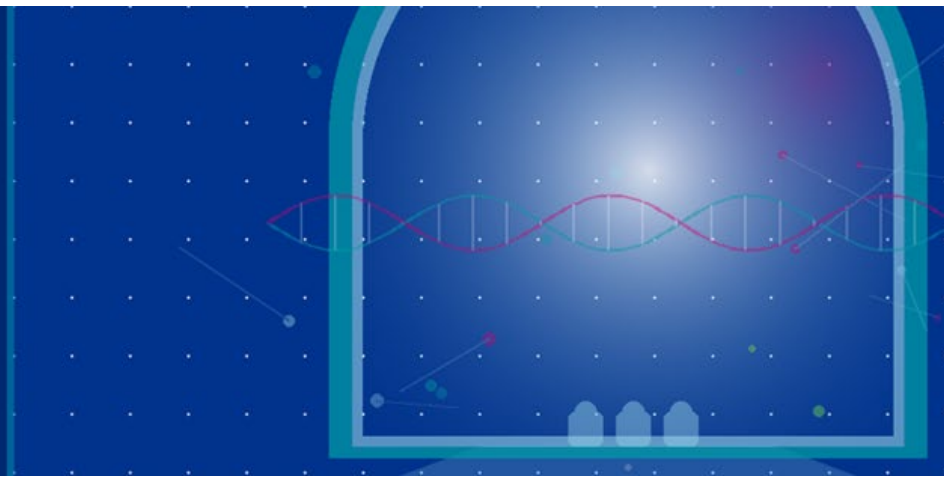


Resiniferatoxin (RTX) for Treatment of Vestibulodynia Pain

Michael Iadarola, Senior Research Scientist, Clinical Center
Mentor: Andrew Mannes
Authors: Michael Iadarola;* Matthew Sapio; Chailee Moss; Tracy Williams; Andrew Mannes

Abstract: Vestibulodynia remains a pervasive and debilitating chronic pain condition in women that is characterized by provoked localized pain at the vulvar vestibule upon touch or pressure. Provoked vestibulodynia is estimated to affect 10-12% of women in the general population. Affected patients have significantly limited clothing choices, general activities, sexual function, and overall quality of life. Available treatments are not mechanism-based, vary in effectiveness, and in refractory cases, may include irreversible excisional surgery. We propose a new approach that treats neural pathology directly, preserves tissue, and has the potential to permanently normalize or "reset" peripheral nociceptive input to yield long term remission. To achieve this aim, we will conduct a clinical trial of a drug treatment designed to selectively silence hyperactive pain-producing nerve endings in vestibular skin without affecting other sensations such as cold, touch, pressure, or motor functions. The agent, called resiniferatoxin (RTX), is isolated from the plant Euphorbia resinifera. RTX causes prolonged inactivation of pain-sensing nerve endings by binding to the heat- and inflammation-sensitive ion channel TRPV1. These nerve terminals are known to hyper-proliferate in affected vestibular skin and their selective removal allows regeneration of normal nerve fibers to resolve the disorder. We know in patients with cancer pain and nerve-injury-induced neuropathic pain that a single RTX treatment produces significant, long-duration analgesic actions yet preserves other sensory functions. This intervention can transform vestibulodynia care from chronic symptom management or surgical intervention to a targeted, sensory-sparing, disease-modifying therapy that meaningfully impacts quality of life and restores reproductive health.

Keywords: Vestibular pain; TRPV1; Chemoablation

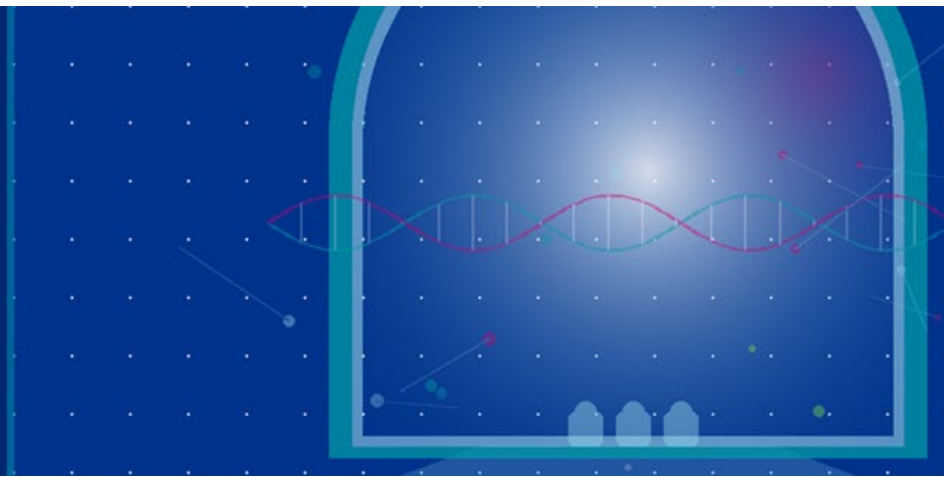


Sex Differences in Alcohol Use and Its Relation to Current vs Remitted Major Depressive Disorder

Sun Jung Kang, Staff Scientist, National Institute of Mental Health
Mentor: Kathleen Merikangas
Authors: Sun J Kang,* Kevin Conway, Marie-pierre F Strippoli, Martin Preisig, Kathleen R Merikangas

Scientific Background: Sex differences in major depressive disorder (MDD) are well documented, but the role of alcohol consumption in modulating these differences, particularly between current and remitted MDD, is not fully understood. Investigating how alcohol interacts with sex in relation to depressive states may offer insights into sex-specific factors associated with MDD.
Research Question(s) / Hypothesis: This study aimed to explore the association between sex and MDD (lifetime, current, and remitted), the impact of alcohol on MDD, and whether sex modifies the relationship between alcohol and MDD.
Experimental Design / Methodology: Cross-sectional data from the population-based CoLaus study (n=2317) were analyzed. Logistic regression models tested the associations between sex, alcohol consumption (moderate and heavy), and MDD (lifetime, current, and remitted), adjusting for age, BMI, smoking, anxiety, and medication use. Interaction terms between sex and alcohol were examined, and stratified analyses were performed.
Results: Sex was significantly associated with remitted MDD, but not with current MDD in the adjusted model. A significant sex and heavy alcohol consumption interaction emerged for current MDD. Stratified analyses showed alcohol consumption was negatively associated with current MDD in men, but not in women. Conversely, BMI, smoking and anxiety were positively associated with current MDD in women, but not in men.
Conclusions and Implications: Alcohol consumption and smoking differentiate current from remitted MDD in a sex-specific manner, suggesting that these substance-use behaviors may help explain sex differences in depressive states. Further research is needed to understand the mechanisms behind these sex-specific associations and their implications for targeted interventions.

Keywords: Current Vs Remitted Major Depressive Disorder

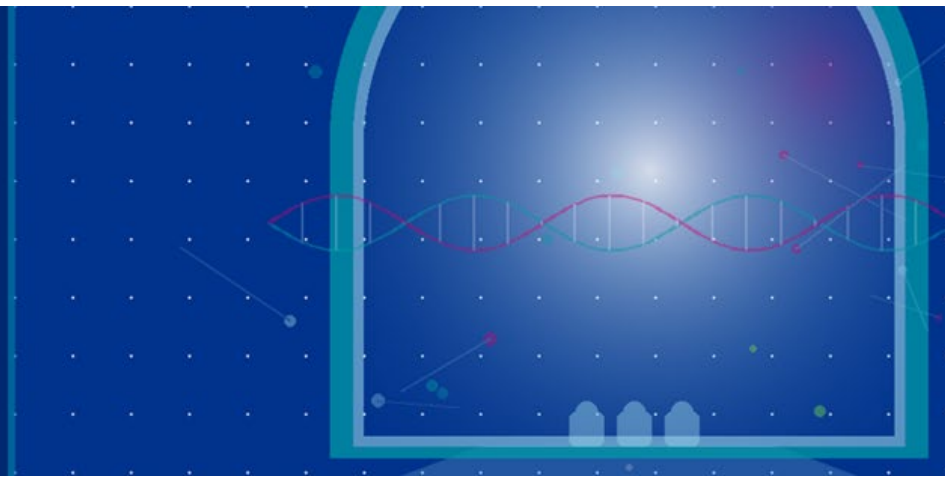


Sexual Dimorphism in Hepatic Lipid Droplet Composition in a Mouse Model of MASLD

Lila Gonzalez Hodar, Visiting Fellow, National Institute of Diabetes and Digestive and Kidney Diseases
Mentor: Yaron Rotman
Authors: Lila Gonzalez-Hodar;* David Kleiner; Yaron Rotman

Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a chronic and heterogeneous condition affecting approximately 25% of women worldwide. Despite its high prevalence and clinical significance, therapeutic options remain limited, and its pathophysiology is not completely understood. Mouse models are essential for elucidating MASLD pathophysiology; however, these models exhibit marked sexual dimorphism, with female mice accumulating liver fat (steatosis) more slowly and less severely than males. The mechanisms driving these sex differences remain unclear. A defining feature of MASLD is the accumulation of triglycerides (TG) within hepatocyte lipid droplets (LDs). Emerging evidence suggests that LD lipid composition influences lipotoxicity and liver injury. Therefore, this study aimed to characterize sex-specific differences in hepatic LD lipid composition and morphology in a diet-induced MASLD model. Male and female C57BL/6J mice were fed a high-fat diet (HFD) for 8 weeks. Hepatic LDs were isolated using sucrose gradient ultracentrifugation and analyzed by LC-MS/MS (lipidomics). Liver histology was assessed by hematoxylin and eosin staining, with steatosis scored by a pathologist blinded to sex. Hepatic TG content was quantified using a colorimetric assay. After 8 weeks of HFD, males exhibited significantly higher steatosis scores than females (67.1% vs. 16.6%), as expected. Consistent with histological findings, total hepatic TG levels were 6-fold lower in females. Liver TG in females was distributed preferentially in the form of macrosteatosis, with a large single lipid vacuole per hepatocyte, whereas the male livers presented a mixture of macro and microsteatosis, with multiple small vacuoles per cell (2.3-fold, p=0.008). Lipidomic analysis of isolated hepatic LDs revealed that female LDs contained significantly less TG (2.3-fold lower) but were enriched in cholesterol esters (CE) (3-fold higher), phosphatidylcholine (PC) (1.4-fold higher), and sphingomyelin (SM) (1.4-fold higher) compared to males. In conclusion, male and female mice exhibit marked differences in hepatic lipid content, distribution, LD size and LD lipid composition in diet-induced MASLD. Female LDs are characterized by a neutral core enriched in CE and a monolayer enriched in PC and SM. These results provide insight into the mechanisms underlying sexual dimorphism in MASLD and underscore the importance of incorporating both sexes in preclinical MASLD research.

Keywords: MASLD, lipids, Sexual dimorphism

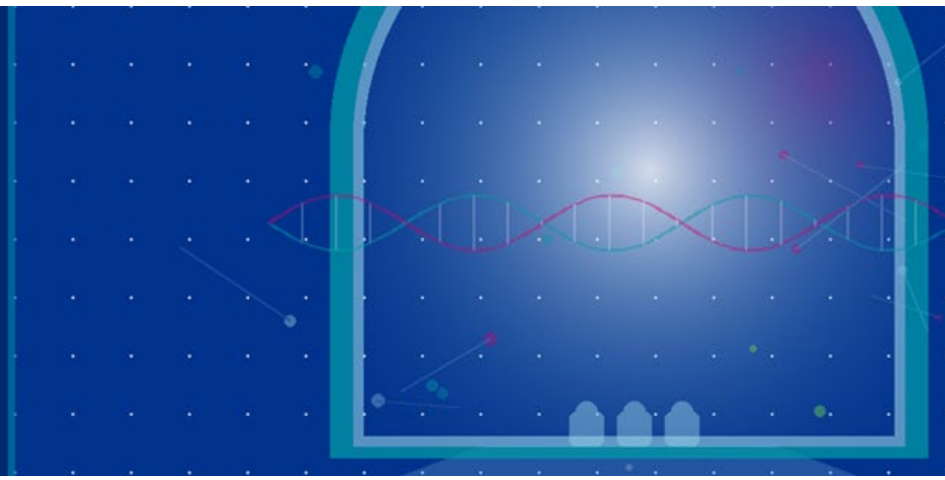


Soluble Adenylyl Cyclase Inhibitors Attenuate Interferon Activation in Human Pulmonary Artery Endothelial Cells

Kadija Hersi, Staff Clinician, National Heart, Lung, and Blood Institute
Mentor: Jason Elinoff
Authors: K. Hersi,* L. Y. Chen, K. S. Awad, C. L. Friend, C. Y. Demirkale, S. Wang, G. M. Graninger, R. D. S. Levent, S. Gurung Pandey, P. Hwang, M. A. H. Siddique, R. L. Danner, R. Goldbach-mansky, M. A. Solomon, and J. M. Elinoff

Rationale: Pulmonary arterial hypertension (PAH), is a rare female predominate disease that is characterized by obstructive remodeling of the distal pulmonary arteries, resulting in increased pulmonary vascular resistance and consequently right heart failure. Interferons are associated with development, progression and severity of PAH. Caveolin-1 (CAV1) is a multifunctional scaffolding protein that regulates a range of signaling molecules including cAMP-dependent protein kinase (PKA). Loss-of-function mutations in caveolin-1 (CAV1) are a rare cause of hereditary PAH, and in human pulmonary artery endothelial cells (HPAECs), CAV1 deficiency induces type I interferon activation and increases phosphorylation of cAMP response element binding protein (CREB). Here, we investigated the therapeutic potential of targeting upstream regulators of cAMP to reduce interferon activation driven by CAV1 loss in HPAECs.
Methods: CAV1-silenced HPAECs were treated with vehicle or selective inhibitors of transmembrane adenylyl cyclase (tmAC) or soluble adenylyl cyclase (sAC). HPAECs were stimulated with interferon-□ in the presence or absence of sAC inhibitors. Levels of phosphorylated STAT1 were assessed by immunoblotting. RNA was isolated from HPAECs in vitro and peripheral blood mononuclear cells (PBMCs) from PAH patients (n=43) and Healthy controls (n=12). Induction of interferon-regulated genes were determined by RT-PCR and NanoString analysis.
Results: Type I interferon gene scores were higher in PAH patients compared to healthy controls. Inhibition of tmAC did not affect CAV1 deficiency-induced STAT1 activation in HPAECs. However, sAC inhibitors, KH7 and LRE1, attenuated both CAV1 loss-associated and interferon □-induced STAT1 activation. Notably, both KH7 and LRE1 attenuated constitutive interferon-regulated gene activation associated with CAV1-deficiency as well as interferon □-induced gene expression in HPAECs. Importantly, both KH7 and LRE1 also reversed the proliferative phenotype associated with CAV1 deficiency in HPAECs.
Conclusion: Our data implicates a role for sAC in lung endothelial interferon activation and highlights a potential therapeutic target for PAH.

Keywords: Pulmonary arterial hypertension (PAH), Caveolin-1 deficiency associated type I interferon activation, Soluble adenylyl cyclase

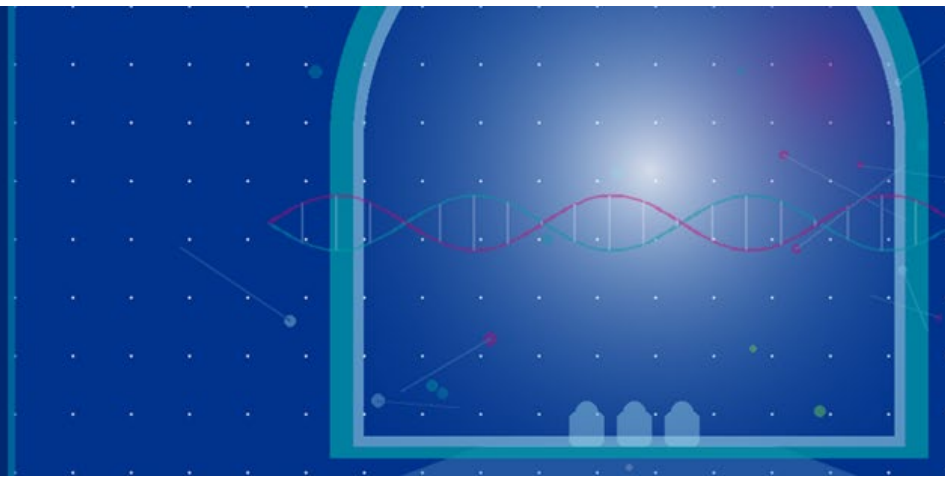


Supporting hypertensive disorders of pregnancy research with evidence mapping – a novel biomarker characterization tool

Brandiese Beverly, Staff Scientist, National Institute of Environmental Health Sciences
Mentor: Andrew Rooney
Authors: Brandiese Beverly;* Vickie Walker; Meredith Clemons; Robyn Blain; Courtney Lemeris; Erin Mcnell; Jo Rochester; Andrew Rooney

Abstract: Hypertensive disorders of pregnancy (HDP) are a leading cause of maternal morbidity and mortality. Risk factors only account for a small percentage of the cases, suggesting a role for other factors, such as environmental exposures. The use of biomarkers for the prediction of HDP is integral to disease stratification and targeted therapy, but the utility, availability, and human relevance of biomarkers studied in animal models remains variable. To support the characterization of key HDP biomarkers, a systematic evidence map (SEM) was developed. The SEM approach utilizes systematic review methods to identify, summarize, and visualize available evidence for complex research questions. The goal of this effort was to characterize biomarkers associated with HDP, determine the extent to which those biomarkers were evaluated in animals, understand the strengths/limitations of HDP rodent models, and identify environmental exposures evaluated in the context of HDP biomarkers. Over 30,000 human and 5,000 animal studies were identified in a comprehensive literature search and screened for relevance. Less than half of human biomarkers were identified for initial strength/weakness analysis as most biomarkers captured in human studies were also evaluated in the rodent models. Further, several rodent models were used to evaluate HDP, including reduced uterine perfusion pressure and transgenic models, with some more appropriate for investigating earlier mechanisms than others. It was clear that evaluation of HDP biomarkers in the context of environmental exposures represents a significant data gap—less than 50 biomarker studies also evaluated an environmental exposure. Interactive evidence maps enable users to search, sort, and filter datasets based on research interest allowing subsets of data to be isolated and associated papers downloaded for further interrogation. This SEM allows for the identification of human-relevant biomarkers that can be used to evaluate the impact of environmental exposures on HDP in animal models, combinations of biomarkers that can be evaluated in the first trimester to support early prediction of HDP, data gaps to inform primary research studies, and pockets of data that might be suitable for full systematic review.

Keywords: Preeclampsia, Hypertension, Pregnancy



TRAIL Induces Cytokine Production Via the Nfkb2 Pathway Promoting Neutrophil Chemotaxis and Neutrophil-mediated Immune-suppression in Triple Negative Breast Cancer Cells

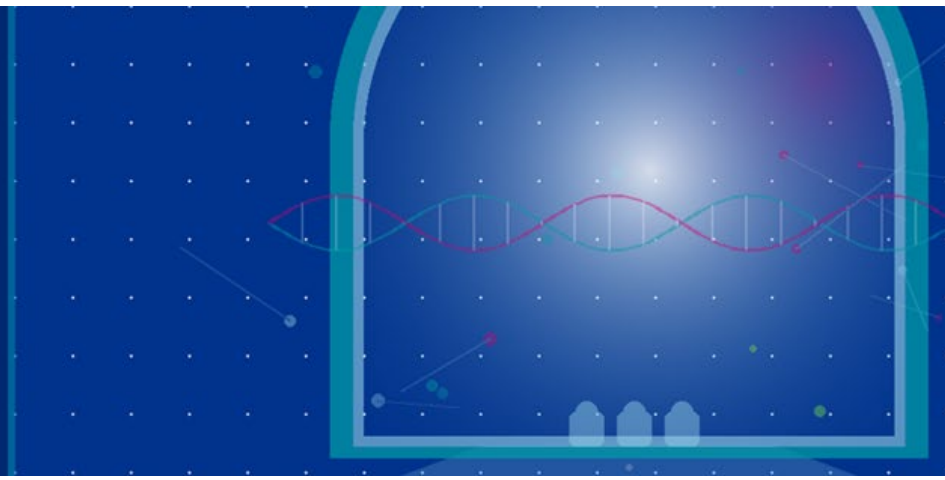
Manjari Kundu Sil, Visiting Fellow, National Cancer Institute

Mentor: Stan Lipkowitz

Authors: Manjari Kundu,* Yoshimi E Greer, Alexei Lobanov, Lisa Ridnour, Renee N Donahue, Yeap Ng, Shashi Ratnayake, Karley White, Donna Voeller, Sarah Weltz, Qingrong Chen, Stephen J Lockett, Maggie Cam, Daoud Meerzaman, David a Wink, Roberto Weigert, Stanley Lipkowitz

Abstract: Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a potential cancer therapeutic that induces apoptosis in cancer cells while sparing the non-malignant cells in preclinical models. However, its efficacy in clinical trials has been limited, suggesting unknown mechanisms modulating TRAIL activity in patients. We hypothesized that TRAIL treatment elicits transcriptional changes in triple negative breast cancer (TNBC) cells that alter the immune milieu. RNAseq analysis of MDA-MB-231 cells along with validation in additional cell lines demonstrated that TRAIL induced cytokines such as CXCLs 1, 2, 3, 8,11 and IL-6, which are known to modify neutrophil function. Mechanistically, TRAIL dependent induction of the cytokines was predominantly mediated by death receptor 5, caspase-8 and the non-canonical NFKB2 pathway. These cytokines produced by TRAIL-treated TNBC cells enhanced chemotaxis of normal human donor isolated neutrophils. Using TNBC xenograft models, TRAIL induced activation of NFkB2 pathway, cytokine production and increased neutrophil recruitment into the tumors. Moreover, preincubation of neutrophils in supernatants from TRAIL-treated TNBC cells significantly impaired neutrophil function as measured by reduced respiratory burst and cytotoxic effect against TNBC cells. Transcriptomic analysis of neutrophils incubated with either TRAIL alone or supernatant of TRAIL-treated TNBC cells revealed increased expression of inflammatory cytokines, immune modulatory genes, immune checkpoint genes, and genes implicated in delayed neutrophil apoptosis. Functional studies showed that these neutrophils suppress T cell proliferation and augment Treg suppressive phenotype. Collectively, our study demonstrates a novel role of TRAIL-induced NFKB2-dependent cytokine production that promotes neutrophil chemotaxis and neutrophil-mediated immune suppression.

Keywords: Apoptosis, Neutrophil-mediated Immune Suppression, Non-canonical Nuclear Factor-kappa B Signaling, Tumor Necrosis Factor-related Apoptosis-inducing Ligand.



Two novel ARL8 effectors, TBC1D9 and TBC1D9B, modulate exosome secretion through the RAB11A-exocyst axis: Mechanism of Cell Cell Communication

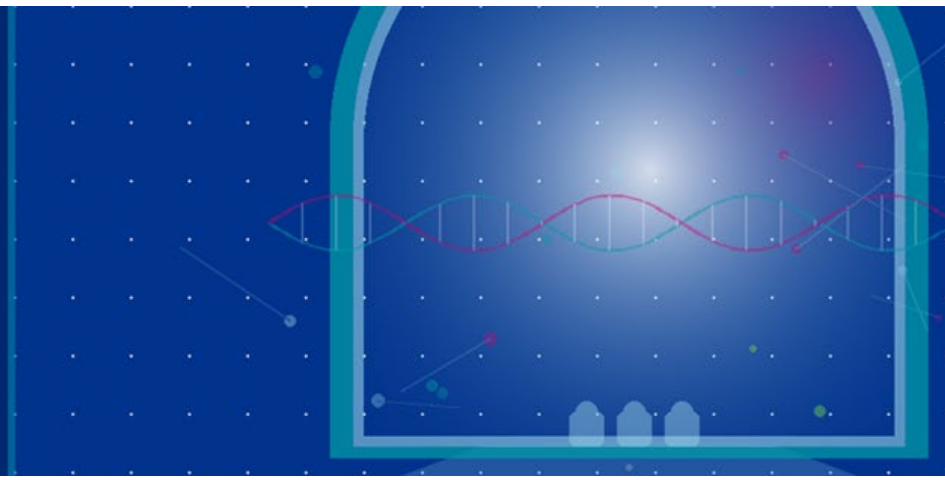
Ganesh Shelke, Visiting Fellow, Eunice Kennedy Shriver *National Institute of Child Health and Human Development*

Mentor: Juan Bonifacino

Authors: Ganesh Vilas Shelke;* Chad D. Williamson; Yan Li; Tal Keren-kaplan; Juan S. Bonifacino

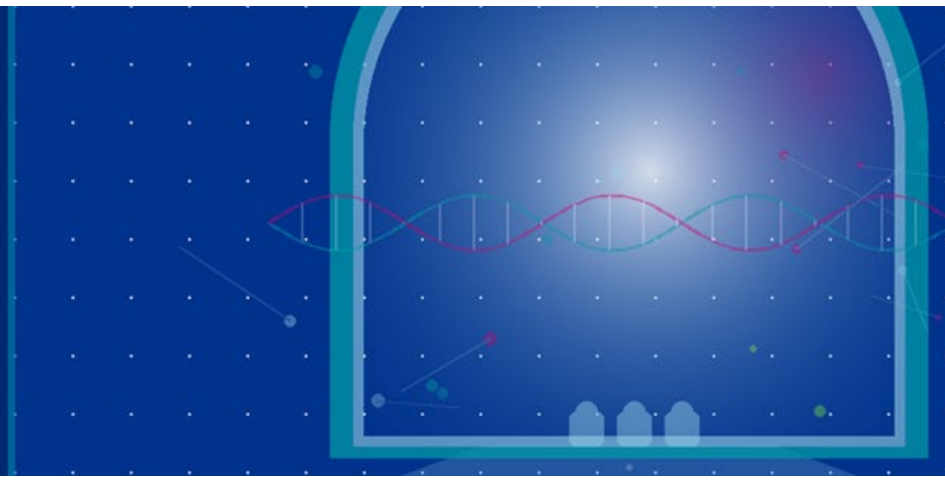
Abstract: Disruptions in endolysosomal function are implicated in neurodevelopmental and neurodegenerative diseases, including Alzheimer's disease, where lysosomal dysfunction increases extracellular vesicle (EV) secretion, contributing to disease propagation. EVs are membrane-bound vesicles that mediate intercellular communication by transporting bioactive molecules. A subset of EVs, known as exosomes, originates from endolysosomal intermediates called multivesicular bodies (MVBs), which fuse with the plasma membrane to release their contents into the extracellular space. The BLOC-One Related Complex (BORC), composed of BORCS1-8 subunits, recruits the small GTPase ADP-Ribosylation Factor-Like 8 (ARL8), enabling Homotypic Fusion and Protein Sorting (HOPS)-dependent fusion of lysosomes with late endosomes and autophagosomes. Previously, I found that the loss of BORC, ARL8, or HOPS results in impaired lysosomal clearance of intraluminal vesicles within MVBs, leading to their increased secretion as exosomes. However, the molecular mechanisms linking BORC and ARL8 to exosome secretion remain incompletely understood. Using proximity biotinylation-based proteomics, I have identified TBC1D9 and TBC1D9B as novel ARL8 effectors. TBC1D9 and TBC1D9B localize to LAMP1-positive endolysosomal compartments in a BORC- and ARL8-dependent manner and function as Rab GTPase-activating proteins (Rab GAPs), inactivating Ras-related protein RAB11A, a key regulator of endocytic recycling. The loss of TBC1D9, TBC1D9B, ARL8, or BORC increases RAB11A membrane recruitment, leading to aberrant activation of its effector proteins, including the exocyst complex, a multi-protein tethering assembly essential for vesicle fusion with the plasma membrane. Knockdown of TBC1D9 and TBC1D9B enhances RAB11A-exocyst interactions, increasing exosome secretion. This suggests that cells compensate for lysosomal dysfunction by rerouting endosomal cargo toward exocytosis. Depleting RAB11A or disrupting the exocyst complex suppresses increased exosome release, confirming that the BORC-ARL8-TBC1D9/TBC1D9B axis controls exosome biogenesis through RAB11A-exocyst interactions. Our findings thus uncover a novel small GTPase cascade through which cells reroute trafficking to balance degradation and secretion. This discovery has potential implications for biomarker discovery and therapeutic development for various diseases including Maternal-Fetal crosstalk.

Keywords: Cell-cell Communication, Extracellular Vesicles, Endosome-lysosome Fusion Stress



Additional NIH Abstracts

* Primary author



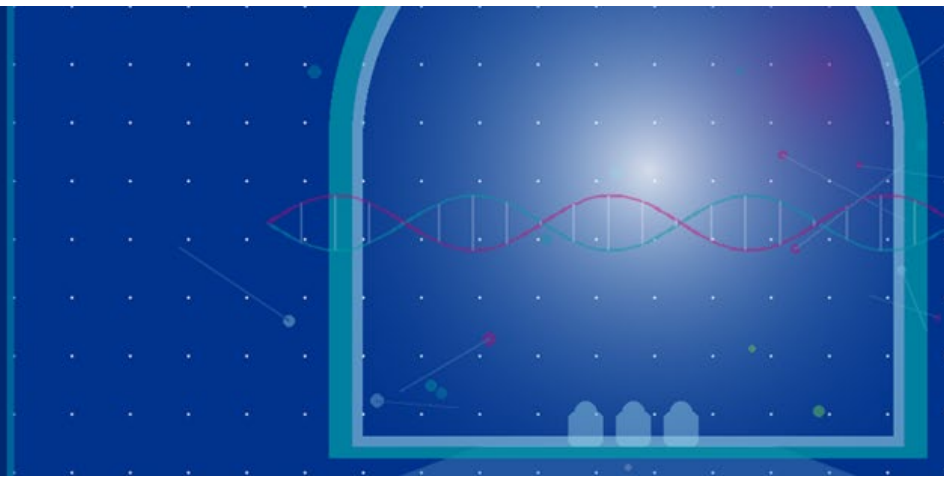
Discover Women's Health Research (DiscoverWHR): Advancing Access and Discovery Through a User-Centered NIH Research Website

Katherine Majewski, DiscoverWHR Federal Lead, National Library of Medicine; Lois Lander, Kiana Roberts (ICF)

Abstract:

The Discover Women's Health Research (DiscoverWHR) website is designed to improve access to and understanding of NIH-supported women's health research by bringing together information from multiple NIH resources into a single, curated entry point. Developed through a collaboration between the NIH Office of Research on Women's Health (ORWH) and the National Library of Medicine (NLM), the website supports NIH's goal of advancing women's health research by enabling efficient exploration of funded projects, clinical trials, curated literature, and common data elements across women's health research areas. DiscoverWHR is intended primarily for early career investigators who are exploring women's health research areas; however, librarians and other researchers who assist with topic exploration, grant planning, and study design will also find the website valuable for their work. By organizing content around research areas that uniquely, disproportionately, or differently affect women across the life course, the website helps users quickly understand the scope of NIH investment and evidence within specific domains of women's health research.

Since its launch, DiscoverWHR has evolved through a user-centered, iterative approach that is informed by ongoing user research with researchers, librarians, and NIH stakeholders. Insights from this research have guided updates to content organization, research area navigation, and contextual framing. These efforts are complemented by close collaboration with subject matter experts across academia and NIH to ensure scientific accuracy, consistent terminology, and alignment with emerging women's health research priorities. A standardized prioritization process that integrates user needs, ORWH priorities, and feasibility considerations to support sustainable growth guides the evaluation and development of new research areas. This approach will guide future enhancements, including access to datasets and related research resources to further support discovery, analysis, and reuse across women's health research areas.



Empowering the Next Generation of Women's Health Researchers

Carolyn Bondar, Marquitta White, Benjamin Johns, Xenia Tigno, NIH Office of Research on Women's Health

Purpose: A recent NASEM report highlighted the need to have a 'robust and productive' women's health research workforce, citing inadequate support for career development in women's health research as a primary cause of the current deficiency in this area. This poster presentation describes NIH's Office of Research on Women's Health's (ORWH) efforts to develop the women's health research workforce and presents an evaluation of three of ORWH's sponsored programs.

Methods: The NIH ORWH collected data from NIH's IMPACII database and conducted surveys related to three programs: the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) program, the Reentry, Reintegration, and Retooling Supplements (RRRS), and Research Supplements to Promote Research Continuity and Retention of Early-Career Biomedical Investigators (Continuity). Outcome metrics include success in obtaining further NIH funding and satisfaction with the program.

Results: The BIRCWH program resulted in about 60% of supported BIRCWH scholars obtaining NIH funding within five years of completing the program, with 86% of survey respondents stating their research is at least partially related to women's health, and over 85% reporting they were very or extremely satisfied with the program. Respondents to the survey on RRRS reported that the supplement was critical in enabling them to resume a research career. Recipients of the Continuity supplements were as likely, and, for some categories, more likely to receive subsequent NIH funding than comparable NIH supported researchers, despite experiencing a career disrupting life event.

Conclusions: ORWH's efforts to build the women's health research workforce show that the programs have been successful in retaining researchers. However, more programs, both sponsored by NIH and led by research institutions, are needed to build a full women's health research workforce.

Keywords: Workforce; career development

A Focused Effort on Understanding, Reducing, and Treating Chronic Disease in US Women

Annina Burns, Health Science Policy Analyst, NIH Office of Research on Women's Health

Authors: Annina Burns;* Elizabeth Barr

Purpose: As part of longstanding efforts to address chronic disease in women, the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH) led development of the first-ever NIH funding opportunities specific to chronic conditions in women, which are important causes of morbidity and mortality in the United States. ORWH partnered with 6 NIH Institutes: NHLBI, NIAMS, NCI, NIA, NICHD, and NIAID. The present study summarizes this funding program in relation to other NIH and ORWH efforts to improve the health of all women.

Methods: Topic, approach, study population, and research type were summarized for the funded awards using publicly available data from the NIH RePORT Expenditures and Results (RePORTER) module and the NIH Research, Condition, and Disease Categorization (RCDC) system. Total spending by mechanism, fiscal year, and Institute was further analyzed.

Results: Across Fiscal Years (FY) 2024 and 2025, a total of 42 awards were made: 21 awards in FY24 (9 R01, 12 R21) and 21 in FY25 (12 R01, 9 R21), for a total investment of over $27M. Funded projects explore a broad range of conditions, including obesity, frailty, endometriosis, menopause, polycystic ovary syndrome, pelvic prolapse, chronic pain, pregnancy, cardiometabolic disease, autoimmune disease, rural health, and mitochondrial function. Multiple research approaches are employed, with awards for basic, translational, clinical, behavioral and social science, epidemiologic, and data science/digital health projects. To date, this funding program has enabled 20 publications, including in high impact journals.

Conclusions: The robust interest in this funding program reflects high enthusiasm from the extramural research community and NIH partners. Awarded projects reflect NIH and HHS priorities related to improving population health, preventing chronic disease, and new approach methodologies. In 2024, the federally mandated Advisory Committee for Research on Women's Health recommended that ORWH continue to expand opportunities to study chronic conditions in women as it relates to prevention, new diagnostics, early intervention, and treatment options for chronic conditions in women; ORWH looks forward to continued collaboration across NIH to achieve this goal.

Keywords: Female-specific conditions, population health, disease prevention

The Institutional Development Award (IDeA) Program on Women's Health Research An NIH-wide Initiative

Regine Douthard, Senior Research Medical Officer, Office on Research for Women's Health

Authors: Regine Douthard,* Balkissa Ouattara, Mihaela Crina Frincu

Purpose: The IDeA Program on Women's Health Research (WHR), led by the NIH Office of Research on Women's Health (ORWH) in partnership with the National Institute of General Medical Sciences (NIGMS) and several NIH Institutes, Centers, and Offices (ICOs), strengthens women's health research capacity in states and territories with historically low NIH funding. The initiative aims to expand women's health research across IDeA-eligible states on a broad range of health issues affecting women across the life course and by supporting studies focused on the prevention, risk reduction, and reversal of chronic diseases affecting women, particularly in vulnerable and rural communities.

Methods: ORWH and NIGMS implemented targeted funding mechanisms to encourage collaboration among institutions and support studies addressing key women's health priorities, including cardiometabolic and chronic conditions across the life course. From FY 2020–2022, three Notices of Special Interest were released to fund one-year administrative supplements supporting women's health research. In FY 2023, NOT-GM-23-012 was issued to provide five-year support through the Centers of Biomedical Research Excellence (COBRE) Phase 1 program, further strengthening state-level women's health research capacity.

Results: Between FY 2020 and FY 2025, the WHR initiative provided $35 million in total funding, including $25.60 million through 90 administrative supplements across 21 states. In FY 2024–2025, four COBRE awards totaling $9.43 million were made to Idaho, Kansas, Louisiana, and Arkansas to establish sustained women's health research centers; two of these programs focus on sex-based precision medicine and the use of big data to advance women's health outcomes. Supported studies focus on major cardiometabolic contributors to morbidity and mortality, pregnancy-related risk factors, and biological links between adiposity, immune dysfunction, and metabolic disease.

Conclusions: Through these investments, ORWH strengthens research capacity, supports local investigators in addressing community-specific health needs, and promotes interdisciplinary collaboration across the IDeA network. These efforts advance research aimed at preventing and reversing chronic conditions in women leaving in IDeA states and across the country.

Keywords: Cardiometabolic, adiposity, immune dysfunction, rural health

Interdisciplinary, Sex-Specific Education for Chronic Disease Prevention in Women

Balkissa Ouattara, Medical Officer, NIH Office of Research on Women's Health

Authors: Balkissa Ouattara,* Elizabeth Barr

Purpose: Chronic diseases are the leading causes of morbidity and mortality among women, yet prevention and management strategies often do not adequately account for sex-specific biology, life-stage transitions, and interdisciplinary care needs. This initiative aims to address these gaps by developing sex-specific, evidence-based educational modules to support prevention and improved management of chronic diseases in women.

Methods: The NIH Office of Research on Women's Health is using a structured, interdisciplinary development framework to design short (10-minute) online educational modules on chronic conditions affecting women. Module development integrates evidence from NIH-supported research, Sex as a Biological Variable (SABV) principles, peer-reviewed scientific literature, and input from relevant NIH Institutes and Offices. Content incorporates sex-specific pathophysiology, life-stage considerations, prevention strategies, nutrition and lifestyle interventions, mental health integration, and coordinated care models. Parallel versions are being developed for healthcare providers and patients to ensure applicability to both clinical practice and self-management.

Results: Four modules—*cardiovascular disease, diabetes across the life course, chronic pain, and autoimmune diseases*—have been fully developed to date. The cardiovascular disease module has undergone peer review by NIH subject matter experts, and final revisions are currently underway, with publication anticipated in February. Additional modules are in active development using the standardized framework, with early emphasis on cardiovascular disease and diabetes, given their major contribution to chronic disease burden among women.

Conclusion: This ongoing initiative establishes a scalable approach to translating NIH-supported research and peer-reviewed evidence into practical, sex-specific learning tools. By emphasizing prevention, early intervention, and interdisciplinary care, these modules are positioned to improve chronic disease management for women and support NIH and HHS priorities to reduce chronic disease burden through targeted, prevention-focused strategies.

Keywords: Cardiovascular disease, diabetes, chronic pain, autoimmune disease

Intersection of NIH Funding for Selected Chronic Conditions and Women's Health Research Coding

Juliane Caviston, Health Science Policy Analyst, NIH Office of Research on Women's Health

Authors: Juliane Caviston;* Balkissa Ouattara; Elizabeth Barr; Samia Noursi

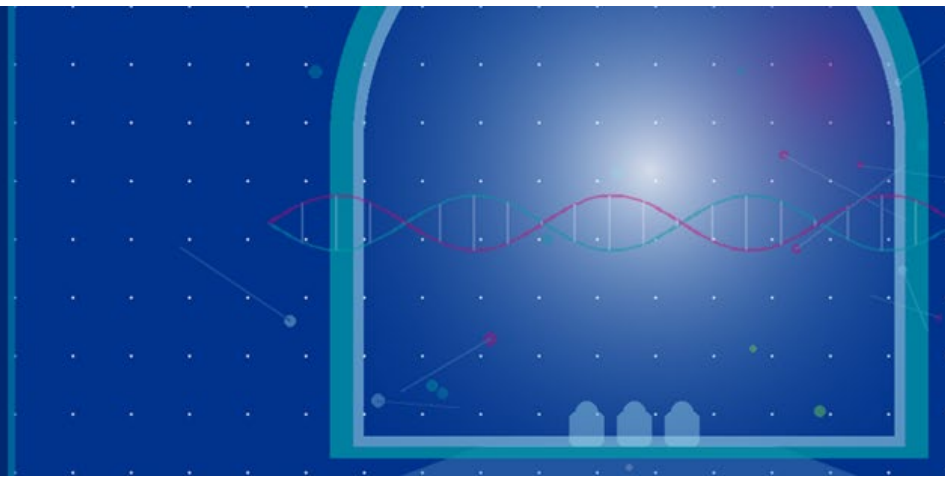
Purpose: NIH moved from manual to automated coding for the NIH Research, Condition, and Disease Categorization (RCDC) Women's Health Research (WHR) category in FY 2024. Automating this category improves its accuracy and consistency in reporting and reduces the administrative burden of manual coding. Using this newly automated WHR RCDC code, ORWH examined NIH women's health research funding for 18 exemplar chronic conditions with high prevalence in women.

Methods: Fiscal year (FY) 2024 funding levels for these conditions were determined using the NIH RePORT Expenditures and Results (RePORTER) database and RCDC codes. For conditions with multiple RCDC codes, one RCDC category was selected for initial analysis. Total FY24 NIH spending at the intersection of each condition and WHR RCDC code was assessed to determine the percentage of total funding for each condition that is also coded as women's health research.

Results: Of the 18 chronic conditions examined, 6 had greater than 10% of their research funding also coded as WHR: infertility, obesity, cancers, mental health conditions, cardiovascular conditions, and alcohol use disorders. The remaining conditions had less than 10% of their research funding also coded as WHR. Four of these conditions – HIV/AIDS, endocrine conditions, chronic pain, and substance use disorders – had between 5% and 10% of research funding coded as WHR and 7 had less than 5%: chronic liver disease, kidney disease, pulmonary conditions, Alzheimer's Disease and related disorders, neurological conditions, arthritis, and autoimmune disease.

Conclusions: This initial environmental scan of the intersection of WHR RCDC coding with chronic conditions funding delivers a snapshot of funding levels for selected chronic conditions in women, providing a baseline and framework upon which NIH can build to identify research opportunities. ORWH will catalyze research for the health of women across the life course consistent with strategic priorities in the NIH Unified Strategy, which includes a sharpened focus on chronic health conditions.

Keywords: Funding; Women's Health Research; female-specific conditions



NIH's Sex as a Biological Variable (SABV) Policy Advances Biomedical Research

Elena Gorodetsky, Research Program Officer, NIH Office of Research on Women's Health

Authors: Elena Gorodetsky,* Chyren Hunter

Purpose: Sex is an independent biological variable with significant impacts across the spectrum of human health and disease. Preclinical research has often used single-sex cells and tissues without justification. Females were frequently not included in human and non-human studies, contributing to real-life health consequences. Moreover, when both sexes were included, results were frequently not analyzed or reported by sex, reducing reproducibility, generalizability, and limiting relevance.

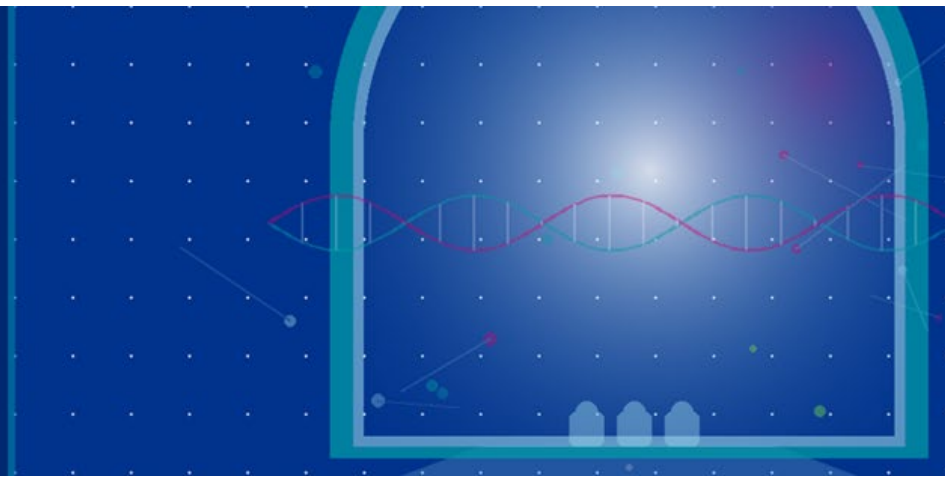
Method: In January 2016, NIH's landmark Sex as a Biological Variable (SABV) policy was published, requiring investigators to consider sex in the study design, analysis, and reporting of vertebrate animal and human studies. A strong scientific justification for single-sex research was required. The NIH Office of Research on Women's Health (ORWH) led the development, implementation, and study of the SABV policy at NIH consistent with its mission to advance women's health.

Results: In the decade since publication of the SABV policy, the consideration of sex influences is increasingly seen as a standard element of research rigor. SABV affects the full research continuum:

- **Basic science:** Minimizes hidden bias by examining sex differences in fundamental pathways.
- **Preclinical research:** Improves the accuracy of disease models and informs more informed go/no-go decisions for translational efforts.
- **Translational research:** Ensures biomarkers and potential treatments are tested in both sexes, leading to more accurate predictions of human responses.
- **Clinical research:** Improves detection of sex differences in efficacy, dosing, adverse effects, and disease symptoms, thereby supporting safer and more effective care for women and men, girls and boys.

Conclusion: Differences between males and females exist at the cellular, tissue, organ, and systemic levels, with impacts on physical and mental health. ORWH continues to advance implementation of the SABV policy through funding, policy guidance, and training resources. Full implementation of the SABV policy entails intentionally integrating sex as a biological variable, thereby improving the rigor, reproducibility, and generalizability of findings and yielding better health outcomes for everyone.

Keywords: Science policy; sex differences



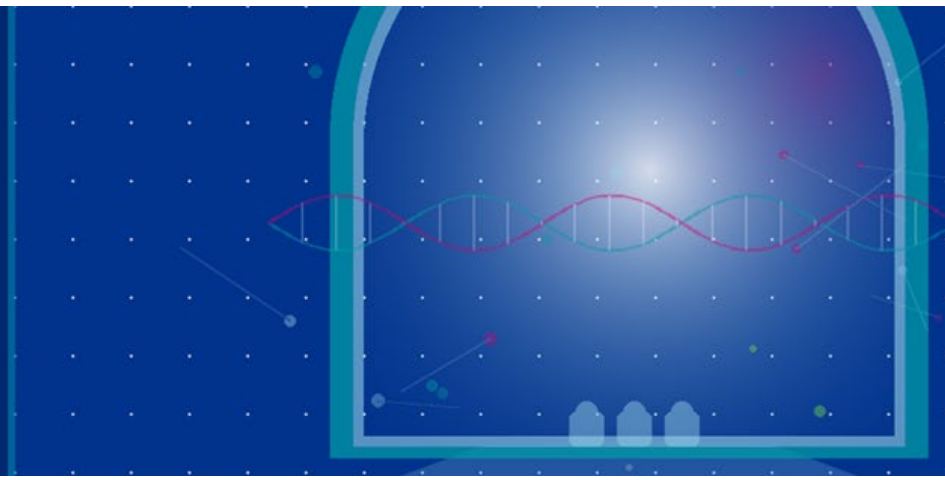
Sex differences in the association between serum micronutrients and bipolar disorder

Raven Hardy Richard, Health Science Policy Analyst, NIH Office of Research on Women's Health

Authors: Raven Hardy Richard,* Elizabeth Barr

Purpose: Sex differences in the presentation and course of bipolar disorder (BD) are well recognized; however, data examining sex differences in biological factors that may influence or modify pathophysiology are limited. Abnormalities in serum micronutrients, including vitamin D, magnesium, vitamin B12, folate, and iron, have been reported in individuals with BD, but whether these measures differ by sex has not been systematically examined. The purpose of this study is to explore sex influence on selected serum micronutrient levels in individuals with BD.
Methods: Cross-sectional data from 1964 individuals with BD (men=621; female=1343; age=20-93 years) within the All of Us (AoU) Research Program was used for this study. Serum micronutrient levels and bipolar diagnosis were obtained from AoU clinical laboratory data; data were extracted on January 29, 2026. A linear mixed-effects model accounting for repeated measures and adjusting for age was used to assess sex differences in mean serum micronutrient levels and likelihood of subnormal micronutrient levels. Adult reference ranges were applied, as sex-specific micronutrient reference ranges are unavailable.
Results: Among individuals with BD, mean serum vitamin D levels were higher in women than in men (33.1 ng/mL [range: 3–206] vs 32.2 ng/mL [range: 4–136]; p=0.01), and women had significantly lower odds of having subnormal vitamin D levels compared with men (OR = 0.45, $p < 0.0001$). In contrast, mean serum magnesium levels were lower in women than in men (1.91 mg/dL [range: 0.3–7.6] vs 1.98 mg/dL [range: 0.6–4.1]; p=0.002), and women had higher odds of subnormal magnesium levels (OR = 1.70, p = 0.0003). No significant sex differences were observed in mean levels or subnormal status for vitamin B12, folate, or iron.
Conclusion: This study found sex differences in mean levels of vitamin D and magnesium for individuals with BD. Additionally, women with BD had lower odds of having subnormal vitamin D levels, but higher odds of having subnormal magnesium levels. Further research is needed to perform a comprehensive assessment and characterize potential associations between serum micronutrients and BD and any clinically relevant sex influences.

Keywords: Vitamin D, bipolar disorder, serum micronutrients



Trends in the Inclusion of Women in NIH-Funded Clinical Research

Dawn Corbett, NIH Inclusion Officer, NIH Office of Extramural Research
Authors: Rebecca Favor, DrPH, CPH, Dawn Corbett, MPH

Introduction: The National Institutes of Health (NIH) has a longstanding commitment to the inclusion of women, members of racial and ethnic minority groups, and individuals across the lifespan in clinical research, as mandated by the NIH Revitalization Act of 1993 and 21st Century Cures Act. We present an analysis of trends in the enrollment of women and recent data on enrollment by age in NIH-funded clinical research.

Methods: We reviewed enrollment data from NIH-funded extramural and intramural clinical research for fiscal years (FY) 2016 through 2025. Data was sourced from NIH's eRA database, which houses interim data submitted by funded researchers. Our analysis focused on trends in enrollment of women, with breakdowns by race and/or ethnicity, age (for FY23-25), and chronic disease research areas using Research, Disease, and Condition Categorization (RCDC) data (for FY25).

Results: From FY16 – FY25, an average of 6.6 million U.S. women enrolled in NIH-funded research annually. Enrollment of racial and/or ethnic minority women ranged from 30% – 38% across the ten-year period, with higher enrollment observed over the last three years. Enrollment of racial and/or ethnic minority women exceeded the enrollment of racial and/or ethnic minority men in all fiscal years except 2017. Across the lifespan, females were enrolled in NIH-funded research approximately equal to males from infancy to approximately 16 years of age. After that, female enrollment was higher compared to males. With the exception of FY17, the proportion of women across NIH's clinical research portfolio was higher than men. Similarly, the proportion of women was higher than men in FY 25 studies focusing on eight of the ten most prevalent chronic conditions. Women make up over 60% of participants in research investigating depression, hypertension, obesity, and osteoporosis, and over 50% in asthma, cardiovascular, chronic obstructive pulmonary disease, and diabetes research. However, in research investigating kidney disease and arthritis, about 43% of participants were women.

Discussion: The data presented provide a clear snapshot of enrollment in NIH-funded research during FY25. However, since these are interim data, they may not reflect final enrollment and enrollment trends may shift throughout the duration of the study. Similarly, aggregate enrollment data may be skewed by large studies, masking differences in enrollment within smaller studies. Age data are limited since the Inclusion Across the Lifespan Policy became effective January 25, 2019, and more comprehensive data have only become available in recent years. Though the enrollment of women in NIH-funded research is above 50% in many areas, the proportions do not yet reflect disease prevalence in some disease areas. This suggests additional work is needed to increase the representation of women in clinical research studies.

Conclusion: NIH has generally been successful in ensuring the inclusion of women in clinical research in alignment with the NIH Policy and Guidelines on the Inclusion of Women and Members of Racial and/or Ethnic Minority Groups in Clinical Research. While women are well-represented in NIH clinical research overall, and among most of the subgroups examined, gaps remain in certain chronic condition and disease areas. Continued focus on the inclusion of women in clinical research is needed to ensure that research findings are generalizable to women and that sex differences are identified.

* Primary author

The NIH Office of Research on Women's Health (ORWH)

Established in September 1990, the NIH Office of Research on Women's Health (ORWH) serves as the focal point for health research at the National Institutes of Health (NIH). For over 35 years, ORWH has worked across NIH and beyond to advance our understanding of biological and social factors influencing women's health and disease, support individuals in biomedical careers, and stimulate research to improve overall health.