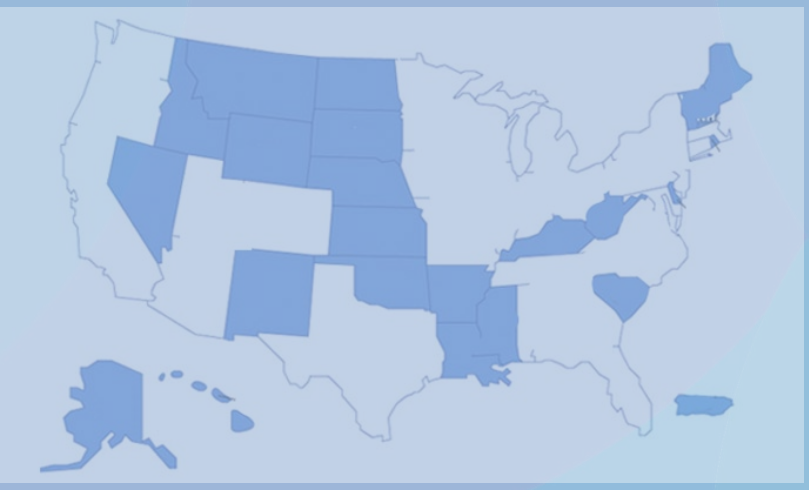
1st NIH Symposium on Women's Health Research in the Institutional Development Award (IDeA) States

June 6, 2024

10 a.m. – 12 p.m. EDT



OVERVIEW

1st NIH Symposium on Women's Health Research in the Institutional Development (IDeA) States

Symposium Purpose

Facilitate networking, knowledge exchange, and recognition of the substantial contributions made by investigators to women's health research within the IDeA States.

Goals

- Engage IDeA investigators who received an administrative supplement for research on women's health in a conversation to share information on their research and research outcomes.
- Bolster the profiles of the administrative supplement awardees and their research on women's health within their institutions and throughout the IDeA programs.
- Highlight program achievements by showcasing the research outcomes reported by IDeA States investigators who have been awarded administrative supplements.

About the IDeA States Women's Health Supplement

Since 2020, the Office of Research on Women's Health (ORWH) has partnered with the National Institute of General Medical Sciences (NIGMS), along with other participating NIH institutes, centers, and offices (ICOs), to advance women's health research and women's health equity by expanding research and research capacity in IDeA States.

IDeA Program and Background

IDeA States are U.S. states (and territories) that are eligible to receive funding from the Institutional Development Award (IDeA) Program. Established in 1993 by congressional mandate, the IDeA Program aims to increase research capacity in states with historically low levels of NIH funding. Managed by NIGMS, the IDeA Program offers multiple types of funding mechanisms that enable institutions in eligible states to jumpstart or bolster their ability to conduct competitive basic, clinical, and translational research. These awards provide research funding as well as support for faculty development and infrastructure improvements that strengthen an institution's biomedical research capacity. Ultimately, the IDeA Program aims to equip institutions to conduct research that addresses the needs of their local communities—particularly those that are medically underserved and/or experience high rates of health disparities. Notably, 5 of the 23 IDeA States rank among the top 10 states with the highest rates of maternal mortality (Arkansas, Kentucky, Louisiana, Mississippi, and South Carolina).

ORWH-NIGMS IDeA Program Partnership

Women's Health Administrative Supplement for Institutional Development Awardees

In 2020, ORWH and NIGMS (with support from other ICOs) partnered to create the first IDeA funding opportunities with a specific focus on women's health and health disparities experienced by women. Together with 14 other NIH ICOs, NIGMS and ORWH issued a Notice of Special Interest (NOSI; NOT-GM-20-017) for administrative supplemental funding, which allowed existing IDeA-funded institutions to apply for 1 year of additional funding to focus on women's health. The opportunity encouraged a broad range of research that addresses important issues of women's health across the lifespan, including maternal and infant morbidity and mortality and their underlying causes.

The response to the NOSI was enthusiastic—more than 37 applications from 20 IDeA States were received. Motivated by this positive response, ORWH, NIGMS, and partner ICOs released similar administrative supplement opportunities in Fiscal Years (FYs) 2021 and 2022. In FY20, 15 IDeA States received awards. In FY21, 11 IDeA States received awards. Awards for FY23 were announced in October 2023 and can be viewed here. As of the close of FY23, 60 grants totaling $16.46 million have been awarded. Since the inception of the Women's Health Administrative Supplement, 21 IDeA States have received awards through this program. ORWH and NIGMS plan to continue to fund IDeA administrative supplements focused on women's health in coming years.

Women's Health COBRE Institutional Development Award

Encouraged by the positive response to the administrative supplements, ORWH and NIGMS partnered again to create a longer-term funding opportunity focused on women's health. In October 2022, they released a new opportunity using the IDeA Program's Centers of Biomedical Research Excellence (COBRE) Phase 1 P20 funding mechanism (NOT-GM-23-012). Through this mechanism, awardees receive funding for three sequential 5-year phases to support the establishment and development of an innovative biomedical research center (a "COBRE"). The COBRE is designed to help institutions develop a critical mass of investigators who can compete effectively for independent research funding and to improve the infrastructure for biomedical research. This long-term model also provides funded institutions with the necessary time and resources to establish and strengthen collaborations with local community organizations so that they can meet the specific needs of the community.

The first NOSI on Supporting Women's Health Research in IDeA States through the Centers of Biomedical Research Excellence (COBRE) Phase 1 Program was released on October 27, 2022. In FY24 three COBREs focused on women's health have been awarded to biomedical research institutions in IDeA States such as Louisiana, Idaho, and Kansas. This effort will expand the distribution of NIH funding for women's health research across the country and advance ORWH's vision for a world in which every woman receives evidence-based disease prevention and treatment tailored to her own needs, circumstances, and goals.

IDeA States Symposium Planning Team

Regine A. Douthard, M.D., M.P.H.
Senior Medical Officer, ORWH
Symposium Co-lead

Crina Frincu, Ph.D.
Program Director, NIGMS
Symposium Co-lead

Balkissa Ouattara, M.D., Ph.D., M.P.H.
Research Medical Officer, ORWH

ICO Leadership

Janine A. Clayton, M.D., FARVO
Director, ORWH
NIH Associate Director for Research on Women's Health

Michele McGuirl, Ph.D.
Acting Director, Division for Research Capacity Building, NIGMS

AGENDA—VIRTUAL EVENT

Virtual Event Page

Opening Remarks -10:00–10:15 a.m. EDT

Welcome	**Dr. Regine Douthard, ORWH Co-Lead**
Opening Remarks	Dr. Janine A. Clayton, ORWH Director and NIH Associate Director for Research on Women's Health Dr. Michele McGuirl, Acting Director, Division for Research Capacity Building, NIGMS

Scientific Session 1 – 10:15–10:55 a.m. EDT

Flash Presentations	**Moderator: Dr. Regine Douthard**
Healthy Moms, Healthy Families	Maribel Campos Rivera, University of Puerto Rico Medical Sciences
Delivery and short-term maternal and fetal safety of vaginally administered PEG-PLGA nanoparticles	Emily S. Day, University of Delaware
Pregnancy complications in the Strong Heart Study	Emily Harville, Louisiana State University Pennington Biomedical Research Center
Genetic variation modifies sex differences in severity of viral infection	Dimitry Krementsov, University of Vermont and State Agricultural College
Maternal health and lifestyle during pregnancy and offspring brain development	Xiawei Ou, Arkansas Children's Hospital Research Institute
Targeting fusin axis in endometriosis-associated ovarian cancer	Nalini Santanam, Marshall University
A pilot study on the impact of the BumptUp® mobile app on physical activity during and after pregnancy	Rachel Tinius, University of Louisville
A need for more than tele-text in postpartum hypertensive women	Kedra Wallace, University of Mississippi Medical Center
Q&A Session	**Moderator: Dr. Balkissa Ouattara**

Scientific Session 2 – 11:05–11:45 a.m. EDT

Flash Presentations	**Moderator: Dr. Crina Frincu**
Maternal and neonatal outcomes in women with metabolic syndrome and substance use disorder	Subha Arthur and Usha Murughiyan, Marshall University
Direct impact of mental stress triggered by confinement on the female heart and its long-term cardiac effects	Diana Cruz-Topete, Louisiana State University Health Sciences Shreveport
Attenuation of maternal obesity in BPH/5 preeclamptic mice prevents cardiometabolic risk in female offspring	Jennifer L. Sones, Colorado State University (previously LSU Pennington)
Explore a heterologous prime-boost vaccination (HetPBV) strategy against *Chlamydia*	Lin-Xi Li, University of Arkansas for Medical Sciences
Epigenetic regulation of miRNA expression and biogenesis in lactotrope cells	Brian Cherrington, University of Wyoming
Mechanism of tumor suppressor function of progesterone receptor in breast cancer	Motoki Takaku, University of North Dakota
My Best Alaskan Life	Allex Mahanna, University of Alaska, Anchorage
Microplastic accumulation in placentas from adverse pregnancy outcomes	Men-Jean Lee, University of Hawaii at Manoa
Q&A Session	**Moderator: Dr. Balkissa Ouattara**

Closing Remarks by Dr. Michele McGuirl – 11:45 a.m.–12:00 p.m. EDT

PRESENTER ABSTRACTS

Healthy Moms, Healthy Families

Maribel Campos Rivera, M.D., M.Sc., M.B.A.-HCM, FAAP, Dipl ABOM, and ACLM
Puerto Rico
Professor, University of Puerto Rico Medical Sciences Campus
Founder and Director, Center for Community Outreach for Health Across the Lifespan
Founder, Emerge

Publication: Mancebo LRL, Valle Moro Y, Colon MK, Rivera MC. 187 Exploring the role of maternal exposure to violence in post-partum weight retention among WIC program participants in Puerto Rico. *Journal of Clinical and Translational Science*. 2023;7(s1):57-58. doi:10.1017/cts.2023.264

Affiliation: PI of the SEPA community and collaborator of PRINBRE. Supplement was funded through The Hispanic Alliance for Clinical and Translational Research (CTR)

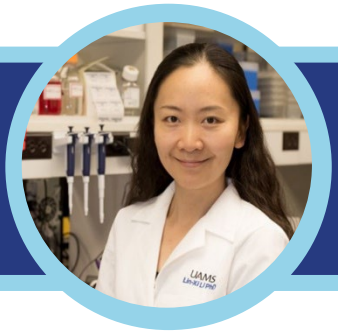
Abstract

Nutritional security during critical life stages such as gestation, postpartum, and early life has been demonstrated to be cost-effective and a significant contribution to social capital. Despite the equitable implementation supported by the WIC program, baseline disparities continue to limit the achievement of minimum requirements for positive health outcomes. The current benefit cliff experienced by families living in Puerto Rico has been demonstrated to result in food insecurity among 51% of low-income families. Our mixed methods cohort study was designed to inform the effects of continued remote service delivery among women enrolled in WIC during the pandemic. The Puerto Rico Department of Health established a strict lockdown in May 2020. Limited compliance with postpartum evaluations demanded the exploration of alternate methodologies to achieve essential health screens. Results from the social determinants of health screening demonstrated that over the previous 12 months, 37.7% of participants had experienced concerns about running out of food, while 31.1% did run out when they did not have money to buy more. When asked about their support system, 22.6% experienced social vulnerability. When we explored the experience of transitioning to services provided during the pandemic, participants acknowledged the impact on daily activities with an appreciation for the increased amount of time spent with family and the capacity to cook at home despite limited access to diverse food. Reduced access to health care was improved by the integration of telehealth, and they are open to implementing IMPLICIT as a strategy to enhance the continuity of care for mothers.

About the Presenter

Dr. Maribel Campos Rivera is a physician scientist, board-certified in pediatrics, neonatal and perinatal medicine, obesity medicine, and lifestyle medicine, with degrees in Health Care Administration and Clinical Research. She is a Robert Wood Johnson Interdisciplinary Research Leaders Alumni with more than 20 years of experience implementing diverse research designs. As a professor at the University of Puerto Rico Medical Sciences Campus, she has mentored trainees at different stages of training and diverse backgrounds, allowing them to meet their community and be better equipped to address the social determinants of health. Her research work focuses on the effects of fetal and early childhood exposures on health across the lifespan. Her trajectory includes community action projects fostering a culture of health through system alignment, science education, and interdisciplinary care. Her team collaborates with community-based and professional organizations to develop and implement evidence-based, place-based, and community-informed solutions. Her role within the Voices for Healthy Kids community, supported by the American Heart Association, is just one example of their contributions toward health equity. She is the founder and director of the Center for Community Outreach for Health

Across the Lifespan and a past member of the Board of Directors of the Puerto Rico College of Physicians and Surgeons as president of the Research and Technological Development Institute up to her appointment as a member of the President's Council on sports, fitness, and nutrition. She is a member of the Nutrition Sub Committee of the Council. Her commitment to improving the adoption rate of healthy lifestyles fueled her transition from NICU medical director to founder of Emerge, a public benefit corporation dedicated to family-centered integrated health care.



Explore a heterologous prime-boost vaccination (HetPBV) strategy against *Chlamydia*

Lin-Xi Li, Ph.D.
Associate Professor, Department of Microbiology and Immunology
University of Arkansas for Medical Sciences (UAMS)

Publications:

Mercado MAB, Du W, Malaviarachchi PA, Gann JI, Li LX. Innate IFN-γ Is Essential for Systemic Chlamydia muridarum Control in Mice, While CD4 T Cell-Dependent IFN-γ Production Is Highly Redundant in the Female Reproductive Tract. Infect Immun. 2021 Feb 16;89(3):e00541-20. doi: 10.1128/IAI.00541-20. PMID: 33257535; PMCID: PMC8097277.

Gann JI, Malaviarachchi PA, Du W, Mercado MAB, Li LX. IFNγ and Antibody Synergize To Enhance Protective Immunity against Chlamydia Dissemination and Female Reproductive Tract Reinfections. Infect Immun. 2022 Dec 15;90(12):e0032822. doi: 10.1128/iai.00328-*22*. Epub 2022 Nov 14. PMID: 36374101; PMCID: PMC9753678.

Mercado MAB, Li Q, Quick CM, Kim Y, Palmer R, Huang L, Li LX. BHLHE40 drives protective polyfunctional CD4 T cell differentiation in the female reproductive tract against Chlamydia. PLoS Pathog. 2024 Jan 25;20(1):e1011983. doi: 10.1371/journal.ppat.1011983. PMID: 38271477; PMCID: PMC10846703.

Affiliation: Department of Microbiology and Immunology, Center for Microbial Pathogenesis and Host Inflammatory Responses (COBRE P20GM103625), University of Arkansas for Medical Sciences (UAMS)

Abstract

Background: *Chlamydia trachomatis* cause the most reported infectious disease in the United States, with more than 3 million new cases occurring annually. This "silent disease" poses serious threats to the reproductive health of young women, while a prophylactic vaccine is currently unavailable. Exploring novel vaccination strategies against *Chlamydia* and identifying immune correlates of protection are essential for the rational design of a much-needed chlamydia vaccine.

Methods: Using various combinations of bacterial (*Listeria monocytogenes*, Lm) and viral (*Lymphocytic choriomeningitis* virus, LCMV) vectors in conjunction of *Chlamydia* antigens, we measured the quantities of circulating memory CD4 T cells and compared the protective efficacy of heterologous and homologous prime-boost vaccination (HetPBV and HomPBV). Moreover, using single cell RNA sequencing (scRNAseq) and TCR profiling, we compared CD4 T cell gene expression profiles and clonality following various vaccination strategies after *Chlamydia* intravaginal challenge.

Results: We observed that HetPBV induced more robust clonal expansion of *Chlamydia*-specific CD4 T cells in the female reproductive tract than HomPBV. Moreover, Lm-based vaccination strategies provide immune protection against *Chlamydia*, whereas LCMV-based vaccines were non-protective. Finally, the LCMV-prime-Lm-boost HetPBV strategy confers the best protective immunity against *Chlamydia* comparable to an AddaVax adjuvanted vaccine.

Conclusions: A viral vector-prime, bacterial vector-boost vaccination strategy holds promise for a protective Chlamydia vaccine. More in-depth bioinformatic analysis is required to identify CD4 T cell gene signatures associated with protective anti-*Chlamydia* immunity.

About the Presenter

Dr. Lin-Xi Li is an associate professor in the Department of Microbiology and Immunology at UAMS. She received her Ph.D. in molecular, cellular, developmental biology and genetics from the University of Minnesota where she trained with Dr. Michael Farrar to study signaling transduction during early B and T cell development. During her postdoctoral training with Dr. Stephen McSorley at the University of California, Davis, she exploited the well-established *Salmonella* infection model to tackle the relationship between erythropoiesis and host susceptibility to *Salmonella*. Meanwhile, she established a new research program investigating antigen-specific CD4 T cell responses to the obligate intracellular bacterium *Chlamydia* in the female reproductive tract (FRT). After joining UAMS in 2015, her research program has been focusing on understanding the protective immune mechanisms in the FRT against *Chlamydia*. Using MHC class II tetramers, we characterized the kinetics and heterogeneity of *Chlamydia*-specific CD4 T cell responses in the FRT and made the unexpected findings that B cells and antibodies are required for optimal CD4 T cell priming and bacterial containment in the FRT mucosa. Moreover, her team reported that IFN-γ production by CD4 T cells are highly redundant for *Chlamydia* control in the FRT mucosa, whereas CD4 T cell polyfunctionality driven by the transcription factor Bhlhe40 is essential for protective immunity. More recently, they expanded their research program to explore novel vaccination strategies against *Chlamydia* and demonstrate that a vector-based heterologous prime-boost vaccination strategy holds promise for a *Chlamydia* vaccine. The ultimate goal of her research is to reveal basic immunological mechanisms to inform the rational design of an urgently needed *chlamydia* vaccine to improve the reproductive health of women. Her research program at UAMS was initially supported by the COBRE Center for Microbial Pathogenesis and Host Inflammatory Responses before she received her own grant support from the National Institute of Allergy and Infectious Diseases.

Maternal health and lifestyle during pregnancy and offspring brain development

Xiawei Ou, Ph.D.
Professor of Radiology and Pediatrics

Publications: Association between Mother's Depression Symptoms during Pregnancy and Newborn's Brain Functional Connectivity. Cerebral Cortex 2023 Jul 5;33(14):8980-8989

Mother's Physical Activity during Pregnancy and Newborn's Brain Cortical Development, Frontiers in Human Neurosciences 2022 Sep 6;16:943341

Maternal Obesity during Early Pregnancy is Associated with Lower Cortical Thickness in the Newborn Brain, AJNR 2021 Dec;42(12):2238-2244

Maternal Anxiety and Depression during Late Pregnancy and Newborn's Brain White Matter Development, American Journal of Neuroradiology 2020, Oct;41(10):1908-1915

Affiliation: University of Arkansas for Medical Sciences (UAMS), Brain Imaging Lab, Arkansas Children's Research Institute, Center for Translational Pediatric Research (COBRE CTPR, PI Alan Tackett, Ph.D.)

Abstract

Background: Human brain development starts soon after conception and progresses rapidly throughout the embryonic and fetal stages and is vulnerable to maternal environmental influences during pregnancy. With recent advances in noninvasive neuroimaging of the developing brain, we can now sensitively detect subtle effects on brain development associated with maternal factors, which may have significant implications on long-term neurodevelopmental outcomes.

Methods: Structural and functional neonatal brain magnetic resonance imaging (MRI) data acquired from the parent COBRE and other projects were processed and analyzed in combination with extensive data of maternal health and

lifestyle during pregnancy. Relationships between maternal factors and offspring brain imaging features were investigated.

Results: Maternal anxiety/depression symptoms during late pregnancy negatively correlated with newborn brain white matter microstructural integrity in frontal and limbic regions; higher depressive symptoms during the third trimester of pregnancy were also associated with lower brain functional connectivity in the frontal lobe and between frontal/temporal lobe and occipital lobe; higher maternal body fat mass percentage measured at early pregnancy was associated with lower cortical thickness in frontal brain regions important for language and executive functions; on the other hand, higher maternal physical activity level during the first and second trimester was associated with greater cortical thickness in frontal and temporal brain regions.

Conclusions: Maternal physical/mental health and lifestyle during pregnancy have significant impacts on offspring brain development. Advanced and innovative informatics approaches will be needed to delineate effects of multiple prenatal factors that may all impact imaging features of the developing brain individually or interactively.

About the Presenter

Dr. Xiawei Ou received his doctoral degree from Vanderbilt University in 2007 with a concentration in MRI physics. He continued his research at Vanderbilt University Institute of Imaging Science as a research fellow before he joined Arkansas Children's Hospital and became a faculty member of UAMS in 2008. Dr. Ou's past research includes development of new quantitative MRI methods and their applications on preclinical and clinical neuroimaging. His current research focuses on developing and implementing advanced pediatric neuroimaging methods to study how different prenatal and early postnatal factors impact the developing brain in children. His research has been funded by NIH, the U.S. Department of Agriculture, the Thrasher Research Fund, the International Society for Magnetic Resonance in Medicine, and other local agencies.

Dr. Ou was one of the inaugural research project leaders for a Phase 1 COBRE (Center for Translational Pediatric Research, PI Alan Tackett, Ph.D.) funded to the Arkansas Children's Research Institute (ACRI), and he successfully graduated with five NIH grants totaling $11.4 million during Phase 1. Since then, he has also served in a number of different roles in other COBRE centers at ACRI and UAMS, including Co-I for a pilot project and a research project at the Center for Childhood Obesity Prevention (CCOP), primary mentor for another pilot project investigator at CCOP, and mentor for a research project leader at the Center for Studies of Host Response to Cancer Therapy.

Epigenetic regulation of miRNA expression and biogenesis in lactotrope cells

Brian Cherrington, Ph.D.
Associate Professor, Department of Zoology and Physiology
University of Wyoming

Publications:

Christensen AO, Li G, Young CH, Snow B, Khan SA, DeVore SB, Edwards S, Bouma GJ, Navratil AM, Cherrington BD, Rothfuss HM. Peptidylarginine deiminase enzymes and citrullinated proteins in female reproductive physiology and associated diseases†. Biol Reprod. 2022 Dec 10;107(6):1395-1410. doi: 10.1093/biolre/ioac173. PMID: 36087287; PMCID: PMC10248218.

Ralston BA, Khan L, DeVore SB, Bronnenberg TA, Flock JW, Sequoia AO, Thompson PR, Navratil AM, Cherrington BD. Peptidylarginine deiminase 2 regulates expression of DGCR8 affecting miRNA biogenesis in gonadotrope cells. Reproduction. 2023 Jul 3;166(2):125-134. doi: 10.1530/REP-22-0482. PMID: 37310889; PMCID: PMC10561559.

Affiliation: Department of Zoology and Physiology, University of Wyoming, Wyoming INBRE

Abstract

Peptidylarginine deiminase (PAD) enzymes epigenetically regulate gene expression in pituitary lactotrope cells; yet the physiological consequences of this on lactotrope function during pregnancy and lactation are unknown. This gap in knowledge is important because lactotrope remodeling during pregnancy is absolutely required to maximize prolactin synthesis and initiate lactation. This is a highly relevant medical question because breastfeeding has profound health benefits for both the mother and infant. Our long-term goal is to understand hormone mediated epigenetic control of lactation at the molecular level. The objective of this project was to show that PAD catalyzed histone citrullination is a novel regulator of miRNA expression and biogenesis that mediates 17β-estradiol (E2) induced lactotrope population changes during pregnancy. PAD expression is highest in lactotropes from late pregnant mice, and these enzymes suppress expression of miRNAs and a riboprotein termed DGCR8 microprocessor complex subunit (DGCR8), which is critical for miRNA biogenesis. We propose a model in which E2 stimulates PAD expression, and then histone citrullination suppresses miRNA expression and biogenesis. With decreased miRNAs, mRNAs encoding important proliferative and growth factor proteins increase to drive lactotrope remodeling during pregnancy. Our central hypothesis is that E2 increases expression of PAD enzymes, which then citrullinate histones to suppress miRNAs in lactotropes during pregnancy. The work is significant because it will help characterize a novel, unexplored mechanism that is essential for lactotrope population changes during pregnancy and ultimately lactation. The proposed research is innovative because investigating the role of histone citrullination on miRNAs represents a new and substantial departure from current studies in the field.

About the Presenter

Dr. Brian Cherrington completed his undergraduate degree at Washington University in St. Louis where he dual majored in history and biology. He then received an M.S. and Ph.D. in reproductive endocrinology from Colorado State University. His graduate work investigated regulatory mechanism controlling expression of the gonadotropin releasing hormone receptor (GnRHR) gene, which is critical for gonadotrope function and ultimately all reproduction. Homologous regulation of GnRHR expression was well known, but his work expanded on this and investigated how activin, a TGFβ family member, increases GnRHR expression. In his first post-doc at the University of California, San Diego he examined how transcription factors such as Oct-1, NeuroD1, Mash1, and Msx1 participate in temporal gonadotropin gene expression during development of the anterior pituitary gland. Dr. Cherrington then completed a second post-doc at Cornell University

investigating the function of PAD enzymes in the mammary gland and breast cancer. His work discovered that in mammary epithelial cells PAD2 converts histone tail arginines into the non-coded citrulline residue, which decondenses chromatin and alters the expression of genes involved in tumorigenesis. He was also the first to show that PAD2 is expressed in mammary tumors across species. He joined the Department of Zoology and Physiology at the University of Wyoming in 2011 and is currently an associate professor. His lab studies the function of PAD enzymes and citrullinated proteins in female reproduction and associated diseases. The first scientific objective of his research group at the University of Wyoming is determining the role of histone citrullination in female reproductive gene expression. Research from his lab shows that in pituitary lactotrope cells, PAD catalyzed histone citrullination regulates the expression of miRNAs Let7c, miR23b, and miR29c. These miRNAs, in turn, regulate the expression of oncogene mRNAs HMGA1, N-MYC, and IFG1 and may contribute to lactotrope expansion during pregnancy, which is required for lactation. The second major scientific objective of his lab is determining the functional role of citrullinated proteins and anti-citrullinated protein antibodies (ACPA) in rheumatoid arthritis (RA). Women have a 3-fold higher incidence of RA as compared to men; yet the underlying mechanism for this sex-based health disparity is unknown. The Cherrington lab is testing whether citrullinated proteins stimulate local ACPA production in the female reproductive tract over the lifespan. A better understanding of the mechanisms that initiate ACPA production in the female reproductive tract are critical for developing novel tools to increase early detection and treatment for women with RA.

Direct impact of mental stress triggered by confinement on the female heart and its long-term cardiac effects

Diana Cruz-Topete, Ph.D.
Associate Professor
Louisiana State University Health Sciences Shreveport

Publication: Dhaibar HA et al. Exposure to Stress Alters Cardiac Gene Expression and Exacerbates Myocardial Ischemic Injury in the Female Murine Heart. Int J Mol Sci. 2023 Jul 1;24(13):10994. doi: 10.3390/ijms241310994. PMID: 37446174; PMCID: PMC10341935.

Affiliation: Louisiana State University (LSU) Health Sciences Center (COBRE 2P20GM121307-06, PI: Dr. Chris Kevil)

Abstract

Background: Every year, over 3 million women in the United States experience an acute myocardial infarction (MI). There is a growing trend in the incidence of MI among women aged 35 to 54, with mental stress recognized as a prognostic factor for worse outcomes in premenopausal women. This study aimed to uncover the role of cardiomyocyte glucocorticoid receptors in MI in the female heart.

Methods: In this study, we used a mouse model to investigate the impact of stress on myocardial injury, focusing on the role of glucocorticoid receptors (GR) in cardiomyocytes. We assessed physiological responses, such as circulating cortisol and estrogen levels, and functional responses through echocardiography. Additionally, we evaluated histological and biochemical markers of cardiac damage and heart failure (HF), including increases in markers of reactive oxygen species (ROS) and cell death.

Results: Our findings suggest that glucocorticoids may inhibit estrogen's cardioprotective effects by blocking estrogen's regulation of antioxidant genes. In female mice subjected to stress, deleting GR in cardiomyocytes significantly reduced infarct size and improved survival rates post-ischemia/reperfusion (I/R).

Conclusions: This study highlights the critical interplay between stress hormones and estrogen in modulating cardiac injury in premenopausal women. Targeting cardiomyocyte GR could represent a novel strategy to alleviate the detrimental effects of stress on cardiac function, potentially improving outcomes for women after an MI.

About the Presenter

Dr. Diana Cruz-Topete obtained her B.S. in chemistry-pharmacy-biology from Universidad de Las Americas-Puebla, Mexico, in 2002. Following that, she pursued her graduate studies at the University of Notre Dame-Indiana and was awarded her Ph.D. in biochemistry in 2008. After completing graduate school, she received postdoctoral training at Ohio University and the National Institute of Environmental Health Sciences. In 2016, she joined the Department of Molecular and Cellular Physiology at LSU Health Shreveport, where she currently serves as an associate professor, specializing in stress signaling and cardiovascular disease.

Her research focuses on investigating the molecular basis for sex differences in stress-driven heart disease and failure. She has extensively studied the mechanisms underlying women's heightened susceptibility to the detrimental effects of psychological stress. Through in vitro and in vivo approaches, her lab has tested the hypothesis that glucocorticoids (primary stress hormones) directly impact the heart and exacerbate stress-induced actions by inhibiting estrogen's regulation of protective pathways in cardiomyocytes involving GR. Their groundbreaking work has highlighted the significance of the interaction between GR and estrogen receptors in the context of ischemia/reperfusion-induced heart damage, and they are further investigating how glucocorticoids affect the female heart by studying the effects of cardiomyocyte and vascular GR using transgenic mouse models.

Additionally, her lab is examining the mechanisms by which GR impede estrogen's protective signaling in cardiomyocytes. Furthermore, she is exploring whether inhibiting ferroptosis (supported by preliminary data obtained through the NIH COBRE supplement and an NIH K01 award) could serve as a potential treatment target to mitigate the adverse effects of stress on the heart.

Genetic variation modifies sex differences in severity of viral infection

Dimitry Krementsov, Ph.D.
Associate Professor, Department of Biomedical and Health Sciences
College of Nursing and Health Sciences
University of Vermont

Publication: Bristy Sabikunnahar, Karolyn G Lahue, Loredana Asarian, Qian Fang, Mahalia M McGill, Laura Haynes, Cory Teuscher, Dimitry N Krementsov. Sex differences in susceptibility to influenza A virus infection depend on host genotype PLoS One. 2022 Sep 16;17(9):e0273050. doi: 10.1371/journal.pone.0273050.

Affiliation: Vermont Center for Immunobiology/Infectious Diseases (VCIID) COBRE 5P30GM118228, PI: Ralph Budd, M.D.

Abstract

Background: Infection with the respiratory pathogen influenza A virus (IAV) causes significant morbidity and mortality each year. More severe disease is seen in women compared with men, but genetic mechanisms underlying this sex difference remain obscure.

Methods: Using IAV infection in a mouse model of naturally selected genetic diversity, namely C57BL6/J (B6) mice carrying chromosomes (Chr) derived from the wild-derived and genetically divergent PWD/PhJ (PWD) mice (B6.ChrPWD consomic mice), we examined the effects of genotype and sex on severity of IAV-induced disease.

Results: Compared with B6, PWD mice were completely protected from IAV-induced disease. This resistance was fully recapitulated in the B6.Chr16PWD strain carrying the PWD-derived allele of Mx1. In contrast, other consomic strains, including B6.Chr3PWD and B6.Chr5PWD, demonstrated greatly increased susceptibility. Notably, B6.Chr5PWD and B6.ChrX.3PWD strains, the latter carrying the distal one-third of ChrX from PWD, exhibited increased morbidity and mortality specifically in male but not female mice. Follow-up analyses focused on B6 and B6.ChrX.3PWD strains

demonstrated elevated viral load in B6.ChrX.3PWD male, but not female mice. Transcriptional profiling demonstrated genotype- and sex-specific gene expression profiles in the infected lung, with male B6.ChrX.3PWD mice exhibiting upregulation of a proinflammatory gene expression program, and altered sex-biased expression of several X-linked genes that represent positional candidates, including Tlr13 and Slc25a53.

Conclusions: Our results identify novel loci on autosomes and the X chromosome regulating IAV susceptibility and demonstrate that sex differences in IAV susceptibility are genotype-dependent, suggesting that future genetic association studies need to consider sex as a covariate.

About the Presenter

Dr. Dimitry Krementsov is the director of the Vermont Center for Immunology and Infectious Disease (VCIID) and associate professor with tenure, Department of Biomedical and Health Sciences, College of Nursing and Health Sciences, University of Vermont. His primary research interest is genetic and environmental control of susceptibility to multiple sclerosis (MS), an autoimmune disease of the central nervous system, and his laboratory's main goal is to bridge the gap between observational epidemiologic studies and cause-and-effect mechanistic understanding of disease pathogenesis by applying unique and genetically diverse mouse models, in controlled experimental settings where both genetic and environmental factors can be directly modulated to demonstrate causation, and further mechanistically dissected at the molecular level.

Since his initial appointment in the department of Biomedical and Health Sciences at the University of Vermont in 2017, he has developed a robust research program supported by extramural funds from NIH and the National MS Society (six major research grants as sole PI), established collaborations across the world and in the United States, and published 15 senior author articles to date (47 publications total). His postdoctoral training, focused on immunogenetics and neuroimmunology, was performed in the Department of Medicine, University of Vermont. His Ph.D. training, focused on cell biology of enveloped virus replication, was performed in the Department of Microbiology and Molecular Genetics, University of Vermont.

Delivery and short-term maternal and fetal safety of vaginally administered PEG-PLGA nanoparticles

Emily S. Day, Ph.D.
Associate Professor, University of Delaware

Publication: Irvin-Choy *et al.* Delivery and short-term maternal and fetal safety of vaginally administered PEG-PLGA nanoparticles. *Drug Delivery & Translational Research.* 2023; 13: 3003-3013

Affiliation: University of Delaware (Delaware Center for Musculoskeletal Research (DCMR) COBRE program, DE-CTR ACCEL program, CTR women's health supplement)

Abstract

Background: Nanoparticle (NP) therapies have displayed success against various conditions in non-pregnant patients, but their use in maternal-fetal health applications needs to be established. Local vaginal delivery of NPs is a promising administration route with the potential to yield high cargo retention in the vagina and improved therapeutic efficacy compared to systemic administration. Here, we investigated the biodistribution and short-term toxicity of poly(ethylene glycol)-poly(lactic-co-glycolic acid) (PEG-PLGA) NPs in pregnant mice following vaginal delivery.

Methods: NPs were loaded with DiD fluorophores for tracking cargo distribution (DiD-PEG-PLGA NPs) or formulated with Cy5-tagged PLGA for tracking polymer distribution (Cy5-PEG-PLGA NPs). The NPs were administered to pregnant mice at gestational day (E)14.5 or 17.5, and cargo or polymer biodistribution was analyzed 24-h later by fluorescence imaging of

whole excised tissues and histological sections. To evaluate toxicity, maternal, fetal, and placental weight were measured as well as the number of resorptions and embryos per litter.

Results: DiD cargo was observed only in the vagina with no gestational differences in biodistribution. In contrast, Cy5-PLGA was observed in vaginas, placentas, and embryos, suggesting the polymer can transport beyond the vagina after cargo release. NPs did not impact maternal, fetal, or placental weight, nor did they alter the number of resorptions or embryos per litter compared to saline-treated mice.

Conclusions: PEG-PLGA NPs can deliver cargo to the vagina without having short-term effects on maternal or fetal growth. These findings warrant future investigation into the use of vaginally delivered nanomedicines for conditions affecting the vagina during pregnancy.

About the Presenter

Dr. Emily S. Day is associate professor of biomedical engineering at the University of Delaware (UD), where she joined the faculty in 2013. Dr. Day is also joint associate professor of materials science and Engineering at UD and serves as associate director of the Institute for Engineering Driven Health. At UD, Dr. Day's team engineers NPs for high precision therapy of diseases including aggressive cancers, hematologic disorders, and reproductive health conditions. She has received several notable honors for her research, including the 2018 Rita Schaffer Award from the Biomedical Engineering Society, an National Science Foundation CAREER Award, Young Innovator/Emerging Investigator awards from four journals (*Cellular and Molecular Bioengineering Journal*, *Nano Research Journal*, *Journal of Materials Chemistry B*, and *Biomaterials Science*), the 2018 Gerard J. Mangone Young Scholar Award from the Francis Alison Society, NIH R35 and R01 grants, and a W.M. Keck Foundation Science and Engineering Grant. Additionally, she was an invited participant in the 2019 National Academy of Engineering Frontiers of Engineering Symposium. In 2022, Dr. Day was named a fellow of the American Institute for Medical and Biological Engineering, and she also received the Mid-Career Faculty Excellence in Scholarship Award from UD that year.

Dr. Day obtained her B.S. in physics with a minor in mathematics from the University of Oklahoma in 2006, graduating summa cum laude. In 2011, she earned her Ph.D. in bioengineering from Rice University, where she worked under the guidance of Dr. Jennifer West to develop NPs for photothermal cancer therapy. While at Rice, Dr. Day received a National Science Foundation Graduate Research Fellowship, a Rice President's Graduate Fellowship, and a Howard Hughes Medical Institute Med-Into-Grad Fellowship. From 2011 to 2013, Dr. Day was a postdoctoral researcher with Dr. Chad Mirkin in the Department of Chemistry at Northwestern University, where she developed RNA-gold NP conjugates to treat brain tumors through gene regulation. Dr. Day received an International Institute for Nanotechnology postdoctoral fellowship and an NIH F32 Ruth L. Kirschstein National Research Service Award postdoctoral fellowship during her time at Northwestern University. Her research at UD builds upon the theme of advancing human health using engineered nanomaterials that was developed during her Ph.D. and postdoctoral training.

Pregnancy complications in the Strong Heart Study

Emily Harville, Ph.D.
Associate Professor
Louisiana State University Pennington Biomedical Research Center

Affiliation: Department of Epidemiology. Tulane University School of Public Health and Tropical Medicine
(IDeA CTR: LACaTS, https://www.lacats.org/, Louisiana Clinical and Translational Science Center, U54 GM104940)

Abstract

Although there are wide disparities in both pregnancy complications and cardiovascular health, most studies addressing the relationship between the two have been conducted in White populations. The Strong Heart Study is a long-running study of cardiovascular disease (CVD) in American Indians from 13 tribes and communities in Arizona, Oklahoma, and the Dakotas. This project collected additional data on pregnancy from medical records, birth certificates, and the Indian Health Service National Data Warehouse. Female participants were asked about their number of livebirths, lost pregnancies, and pregnancy complications. Gestational diabetes was self-reported, diabetes outside of pregnancy was directly measured at regular intervals, and CVD morbidity and mortality outcomes were adjudicated. The analytic dataset consisted of women with self-reported information on gestational diabetes mellitus (GDM) and at least one study visit before pregnancy (n=294) or after pregnancy (n=1710). Cardiometabolic disease was examined using time-to-event analysis with age as the time axis, controlling for covariates (smoking, body mass index [BMI], income, education, age at first birth). Mean age at last follow-up was 59.5 years. Median parity was 4, and 119 (7.1%) women reported a history of GDM for at least one pregnancy. Except for glucose, pre-pregnancy CVD risk factors were not associated with development of GDM or progression from GDM to DM once BMI was accounted for. History of GDM was associated with a higher likelihood of diabetes later in life (aHR 1.98, 95% CI 1.51-2.59), but not with cardiovascular disease, possibly because many participants were still relatively young.

About the Presenter

Dr. Emily Harville is associate professor of epidemiology at Tulane University School of Public Health and Tropical Medicine in New Orleans. Her research interests focus on social and biological causes of adverse pregnancy outcomes, causes of health disparities, and pregnancy within the life course. Because she moved to New Orleans the week before Hurricane Katrina, she has also developed a subspecialty in the effects of disaster on pregnant and postpartum women. She is co-director of the Southern Center for Maternal Health Equity, which aims to test multilevel approaches to improving maternal health in Louisiana and Mississippi. She is principal investigator on an implementation study of an intervention to improve maternal mental health after disaster, as well as a study of reproductive history and cognitive aging, and is involved with efforts to harmonize preconception data across multiple research cohorts. Her teaching interests include epidemiologic methods, epidemiology of health disparities, and data analysis; and she is program director for the Ph.D. in epidemiology. She received her Ph.D. in epidemiology from the University of North Carolina-Chapel Hill in 2005.

Targeting fusin axis in endometriosis-associated ovarian cancer

Nalini Santanam, Ph.D., M.P.H., FAHA
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Marshall University

Publications: Brunty S, Ray Wright K, Mitchell B, Santanam N. Peritoneal Modulators of EZH2-miR-155 Cross-Talk in Endometriosis. Int J Mol Sci. 2021 Mar 28;22(7):3492. doi: 10.3390/ijms22073492. PMID: 33800594; PMCID: PMC8038067.

Brunty S, Mitchell B, Bou-Zgheib N, Santanam N. Endometriosis and ovarian cancer risk, an epigenetic connection. Ann Transl Med. 2020 Dec;8(24):1715. doi: 10.21037/atm-20-2449. PMID: 33490227; PMCID: PMC7812227.

Affiliation: Marshall University, WV-INBRE (PI: Dr. Gary Rankin)

Abstract

Epithelial ovarian cancers are the leading cause of death among women with gynecological cancers. Endometriosis is the growth of endometrial tissue outside the uterus and affects 10-15% of women of childbearing age. Though considered benign, endometriosis shares hallmarks with cancer. An increased risk of ovarian cancer by 30-40% has been reported in women with endometriosis. The mechanisms leading to this increased risk are not known. Our studies showed that exposing human clear-cell ovarian cancer cell lines (TOV-21G) to peritoneal fluid (PF) from women with or without endometriosis increased proliferation and migration as determined by the xCelligence system. There was an increase in EZH2 and H3k27me3 expression as determined by qPCR and WES. The cancer array (Qiagen) showed a significant increase in several inflammatory markers, including the chemokine receptor, CXCR4. The fusin (CXCR4-CXCL12) axis is upregulated in several cancers and endometriotic lesions. CXCR4 is also regulated by EZH2. We hypothesized that PF by modulating the fusin axis increased the growth of ovarian cancer cells. Blocking this axis will block this. TOV-21G cells were exposed to PF in the presence of a CXCR4 antagonist (AMD3100) or EZH2 inhibitor (EPZ6438) or both. The PF increased the expression of CXCR4 and AMD3100 inhibited this; however combining both drugs completely inhibited it. Suggesting that by modulating the CXCR4 axis, the PF increases the growth/migration of ovarian cancer cells. Blocking both pathways inhibited this phenomenon. Future studies will determine whether CXCR4 is directly or indirectly regulated by EZH2. Studies will also be validated using 3D organoids.

About the Presenter

Dr. Nalini Santanam is currently a professor in the Department of Biomedical Sciences and Department of Cardiology (Medicine) at Joan C. Edwards School of Medicine, Marshall University. She completed her Ph.D. from the Christian Medical College, Vellore, India, in 1992 and her M.P.H. from Rollins School of Public Health, Emory University in 2004. Before joining Marshall University, Dr. Santanam worked as a postdoctoral fellow and assistant professor at Emory University School of Medicine and as an associate professor at Louisiana State University Health Sciences Center. At Marshall University, she directs the Cardiovascular Disease Research Cluster, Biomedical Research graduate program. Her research interest is women's health, focusing on cardiometabolic diseases and endometriosis. Her laboratory uses human subjects' samples to investigate the sex differences in epicardial fat function. She also uses animal models to investigate diet/exercise/vaping interventions on the gut-brain-adipose crosstalk. She has been studying the etiology of endometriosis since 1994. Using clinical samples and animal models of pain, her laboratory studies mechanisms involved in endometriosis-associated pain and novel treatment options. Her laboratory also studies the role of endometriosis in increasing the risk of cardiovascular disease and cancer. She has published extensively in these fields and has been funded

through NIH, the American Health Association, and NASA. She serves as the evaluation coordinator of WV-INBRE. She has a long history of mentoring at all levels including undergraduate and graduate students, clinical residents/fellows, and younger faculty. She has directed the American Heart Association–funded undergraduate summer research program at Marshall University since 2015.

A pilot study on the impact of the BumptUp® mobile app on physical activity during and after pregnancy

Rachel Tinius, Ph.D., ACSM-EP, FACSM
Associate Professor, Exercise Science
University of Louisville

Publication: Tinius RA, Blankenship MM, Colao AM, Hawk GS, Perera M, Schoenberg NE. A Pilot Study on the Impact of the BumptUp® Mobile App on Physical Activity during and after Pregnancy. Sustainability. 2022 Oct 1;14(19):12801. doi: 10.3390/su141912801. Epub 2022 Oct 7. PMID: 37840967; PMCID: PMC10574187.

Affiliation: Exercise Science, Western Kentucky University, Kentucky INBRE Network

Abstract

Background: To combat maternal morbidity and mortality, interventions designed to increase physical activity levels during and after pregnancy are needed. Mobile phone-based interventions show considerable promise, and BumptUp® has been carefully developed to address the lack of exercise among pregnant and postpartum women. The primary goal of this pilot study was to test the potential efficacy of BumptUp® for improving physical activity among pregnant and postpartum women.

Methods: A randomized controlled clinical trial was performed (N=35) with women either receiving access to the mhealth app or an educational brochure. Physical activity and self-efficacy for exercise data were collected at baseline (in mid-pregnancy) and at three additional timepoints (late pregnancy, 6 and 12 weeks postpartum).

Results: For moderate-to-vigorous physical activity, a clear trend is observed as the mean estimated difference between groups increases from −0.35 (SE: 1.75) in mid-pregnancy to −0.81 (SE: 1.75) in late pregnancy. For self-efficacy for exercise, the estimated difference of means (control–intervention) changed from 0.96 (SE: 6.53) at baseline to −7.64 (SE: 6.66) in late pregnancy and remained at −6.41 (SE: 6.79) and −6.70 (SE: 6.96) at 6 and 12 weeks postpartum, respectively. When assessing the change in self-efficacy from mid-to-late pregnancy only, there was a statistically significant difference between groups (p=0.044).

Conclusions: BumptUp® (version 1.0 (3)) shows potential for efficacy. Pilot data suggest key refinements to be made, and a larger clinical trial is warranted.

About the Presenter

Dr. Rachel Tinius is an associate professor at Western Kentucky University (WKU) in Bowling Green. She originally joined WKU as an undergraduate student in 2006, and continued her collegiate athletic and academic careers at WKU playing soccer as well as running track and cross country while completing her master's degree in kinesiology. She then moved back to her hometown of St. Louis, Missouri, and obtained a master's degree in science and clinical investigation and a Ph.D. in movement science at Washington University School of Medicine. While at Washington University, she began her work investigating the role of obesity, physical activity, and maternal metabolic health on maternal and infant outcomes. Upon completion of her Ph.D., she returned to WKU as an assistant professor in exercise science. Since arriving at WKU, she has secured continuous external funding through the KY INBRE network and NIH to study physical activity during

pregnancy and postpartum. Dr. Tinius is an American College of Sports Medicine-Certified Exercise Physiologist who has 12 years of experience conducting clinical research with pregnant and postpartum women. She has studied the many effects of exercise during pregnancy on maternal and infant outcomes, as well as designed community-based interventions for pregnant and postpartum women, particularly in marginalized populations. She has published more than 40 peer-reviewed articles on the topic of physical activity during pregnancy, and she presents annually at the American College of Sports Medicine's National Conference, serving as a member of the executive committee for its Pregnancy and Postpartum Special Interest Group (slated to be president in 2028). Over the past several years, her research has led her down the path of innovation as she discovered a need for evidence-based exercise interventions among pregnant and postpartum women. Because of this, she has developed a mobile app, BumptUp®, and started a company, BumptUp Labs, with the mission to bring trustworthy physical activity guidance to all women during and after pregnancy.

A need for more than tele-text in postpartum hypertensive women

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John D. Bower School of Population Health
Professor, School of Medicine, Department of Pharmacology & Toxicology
Professor, School of Medicine, Department of Obstetrics & Gynecology
University of Mississippi Medical Center

Publication: Moustafa ASZ et al. Report from a text-based blood pressure monitoring prospective cohort trial among postpartum women with hypertensive disorders of pregnancy. BMC Preg Childbirth. 2024:24(1)340

Affiliation: University of Mississippi Medical Center, Jackson (Mississippi Center of Excellence in Perinatal Research COBRE)

Abstract

Background: Hypertensive disorders of pregnancy are a main cause of maternal morbidity and mortality with 60% of maternal deaths in the United States occurring during the postpartum period. The utilization of telehealth modalities such as home blood pressure monitoring has shown improvement in blood pressure control and adherence with follow up visits. Our study sought to determine if standardized education improved patient hypertension knowledge and when combined with home blood pressure telemonitoring increased participants' postpartum visit attendance.

Methods: This is an Institutional Review Board approved prospective cohort study conducted at the University of Mississippi Medical Center. Women with a hypertensive disorder of pregnancy who met the inclusion criteria and provided written informed consent to participate were enrolled. Participants received a baseline pre-education questionnaire designed to assess their knowledge of their hypertensive diagnosis, hypertension management, and postpartum preeclampsia (PreE). Participants then received postpartum hypertension education and training on how to use a blood pressure monitor. Remote home blood pressure monitoring was performed via text messages for 6-weeks postpartum. At the conclusion of the study, participants repeated their original questionnaire.

Results: 250 women provided informed consent to participate in the study and were included in this analysis. Relative to the baseline survey, there was a significant increase (p=0.0001) in the percentage of correct responses. There was not an association between study engagement and percentage of correct responses on end of study questionnaire (p=0.33) or postpartum visit attendance (p=0.69).

Conclusions: Implementing a standardized postpartum education session was associated with improvement in patient's knowledge.

About the Presenter

Dr. Kedra Wallace attended Millsaps College in Jackson, Mississippi. After completing her biology degree, Dr. Wallace received an M.S. in pharmacology and toxicology from the University of Mississippi Medical Center (UMMC), a Ph.D. in neuroscience from UMMC, and a postdoctoral fellowship in obstetrics and gynecology.

After completing her postdoctoral fellowship, Dr. Wallace joined the faculty at UMMC as an assistant professor in the Department of OB/GYN. Since that time, she has served as director of research for the Department of OB/GYN, program director for the Master's in Science in Clinical Investigator Graduate Program, and track director for the Maternal-Fetal-Medicine Graduate Fellowship Program.

Today Dr. Wallace is a tenured professor at UMMC with appointments in the departments of Pharmacology & Toxicology and OB/GYN. She also serves as the associate dean of academic affairs and faculty affairs for the John D. Bower School of Population Health at UMMC. Her lab, which has been continuously funded since 2014, is composed of undergraduate students, graduate students, and scientific staff. Dr. Wallace's research team conducts basic science, and clinical, translational, and population research focusing on (1) the neurological relationship between inflammation during pregnancy and postpartum mental health and (2) the relationship between sociocultural influences and health literacy among reproductive aged women.

Maternal and Neonatal Outcomes in Women with Metabolic Syndrome and Substance Use Disorder

Subha Arthur, PhD, Associate Professor
Usha Murughiyan, MD, Clinical Project Lead, Assistant Dean for Clinical Research and Medical Director, Marshall Clinical Research Center (MCRC)
Department of Clinical and Translational Sciences, Joan C. Edwards School of Medicine, Marshall University

Publication: Sundaram, V.L.; Lamichhane, R.; Cecchetti, A.; Arthur, S.; Murughiyan, U. Maternal and Neonatal Outcomes in Women with Metabolic Syndrome and Substance Use Disorder. *Life*. 2023 Sep 19;13(9):1933. doi: 10.3390/life13091933. PMID: 37763336; PMCID: PMC10533184.

Affiliations: Department of Clinical and Translational Sciences, Joan C. Edwards School of Medicine. Marshall University, Huntington WV 25703. COBRE: Appalachian Center for Cellular transport in Obesity Related Disorders (ACCORD). P20GM121299; PI: Dr. Uma Sundaram

Abstract

Background: Metabolic syndrome amplifies the risk of gestational diabetes, preeclampsia, and preterm labor in pregnant women. Similarly, women with substance use disorder (SUD) have worsened obstetric and birth outcomes. Despite these two conditions being major health care disparities in Appalachia, the health outcomes of this cohort have not been studied thus far. This study looks at the health outcomes of this cohort.

Methods: In this retrospective cohort study, we analyzed 27,955 mothers who delivered at Cabell Huntington Hospital between January 2010 and November 2021. We implemented Chi-square tests to determine the associations and multiple logistic regression methods for comparison after controlling for other factors.

Results: We found that MetS, together with SUD, significantly increases the risk as well as the number of pregnancy complications such as gestational diabetes (p<0.001), preeclampsia (p<0.001), premature rupture (p<0.001), preterm labor (p<0.001), and newborn disorder (p<0.001) compared to the women who had none or had either MetS or SUD alone.

Conclusions

- MetS alone causes more complications than SUD during pregnancy.
- Complications were significantly elevated in pregnant women with both MetS and SUD.
- It is important to provide counseling and other forms of clinical interventions to ideally control both MetS and SUD during pregnancy in Appalachian women to improve health outcomes. If not able to control both parameters, at least MetS modifiable parameters such as IR, HTN, DM should be promptly addressed during pregnancy.

About the Presenters

Dr. Subha Arthur

Dr. Subha Arthur's research focus for over a decade has been on intestinal nutrient absorptive transport processes, particularly glucose, amino acids, and bile acids. Her work aims to understand the functional and molecular regulation of intestinal nutrient transporters in pathological conditions like inflammatory bowel diseases.

As an associate professor at Marshall University School of Medicine, Dr. Arthur works in West Virginia, a state facing significant health disparities with obesity and drug addiction being the two most prevalent issues. This reality has become a central focus of her current research.

Funded by the NIH NIGMS Center of Biomedical Excellence (COBRE) Appalachian Center for Cellular Transport in Obesity Related Disorders (ACCORD), Dr. Arthur pursued research on altered cellular transport physiology in obesity-related disorders. Specifically, she investigated alterations in intestinal bile acid absorption in obesity-associated dyslipidemia.

Furthermore, a COBRE-funded supplementary grant facilitated a study titled "Maternal and Neonatal Outcomes in Women with Metabolic Syndrome and Substance Use Disorder in Appalachia." This research aimed to gain a deeper understanding of the health disparities affecting women in Appalachia.

Beyond her current research interests, Dr. Arthur serves as the director of the Molecular and Cellular Physiology Core of the COBRE ACCORD. This core provides technical expertise, equipment, and personnel to investigators within COBRE ACCORD and Marshall University who work with animal models of obesity and related metabolic disorders such as diabetes, hyperlipidemia, and cardiovascular diseases. The core facility not only facilitates obesity-related physiology research but also fosters collaboration and synergy among COBRE ACCORD investigators, pilot grant awardees, and Marshall University researchers interested in various aspects of obesity research related to Appalachian health disparities.

Dr. Arthur's dedication extends beyond research. She is actively involved in teaching and mentoring graduate and medical students, as well as postdoctoral researchers at Marshall University.

Dr. Usha Murughiyan

Dr. Usha Murughiyan currently serves as the assistant dean for clinical research and medical director of the Marshall Clinical Research Center (MCRC) at the Joan C. Edwards School of Medicine (JCESOM) of Marshall University. The MCRC's mission is to promote clinical and translational research throughout the medical school and make clinical trials available to residents of West Virginia and the Tri-State (West Virginia, Ohio, and Kentucky) area of central Appalachia. In this leadership role, Dr. Murughiyan supervises all aspects of clinical trials at Marshall University, including both industry-sponsored and investigator-initiated studies.

Dr. Murughiyan's expertise extends beyond the MCRC. In 2020, she was appointed director of the Translational Science Core (TSC) of the Center of Biomedical Research Excellence (COBRE), COBRE Appalachian Center for Cellular transport in Obesity Related Disorders (ACCORD, P20GM121299-01A1). This core provides services to promote translational and clinical research for faculty, trainees, and students at the University.

Dr. Murughiyan is also dedicated to training the next generation of clinical researchers. She currently teaches and directs the course on Clinical Translational Science – Basic Research Operations (CTS 620) at JCESOM.

Recognizing obesity and addiction as major health care issues in West Virginia, Dr. Murughiyan leveraged her background in OB/GYN to collaborate with Dr. Arthur on a COBRE supplement grant. Her research focused on modifiable parameters in obese pregnant women with addiction, titled "Maternal and Neonatal Outcomes in Women with Metabolic Syndrome and Substance Use Disorder in Appalachia." This recently published study yielded promising findings on potentially modifiable conditions to improve outcomes. Their future goals include studying a larger cohort and potentially conducting a prospective clinical trial to refine these parameters during pregnancy and improve outcomes for women. The impact of this research extends beyond West Virginia, with potential benefits for underserved populations in other rural and urban areas with similar demographics.

Dr. Murughiyan is committed to making translational research more accessible for investigators and students, ultimately aiming to improve the quality of care available to the underserved population of West Virginia.

Attenuation of maternal obesity in BPH/5 preeclamptic mice prevents cardiometabolic risk in female offspring

Jenny L. Sones, Ph.D.
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Publication: Beckers, K.F., Schulz, C.J., Flanagan, J.P., Adams, D.A., Gomes, V.C.L., Liu, C.C., Childers, G.W., Sones, J.L. (2022) Sex specific effects of maternal weight loss on offspring cardiometabolic outcomes in the obese preeclamptic-like mouse model, BPH/5. *Physiological Reports* 10:(17) e154444. PMID: 36065848

Affiliations: Colorado State University College of Veterinary Medicine and Biomedical Sciences, Department of Clinical Sciences, Fort Collins, CO (NIH COBRE P20GM135002, 2020-2023). ***Previously*** *Louisiana State University School of Veterinary Medicine, Department of Veterinary Clinical Sciences and Pennington Biomedical Research Center, Baton Rouge, LA*

Abstract

Background: Preeclampsia (PE) is a hypertensive disorder of pregnancy with effects on offspring, including increased incidence of cardiometabolic disease. We hypothesize that a maternal obesogenic environment influences pregnancy outcomes and offspring cardiometabolic disease in a sex-dependent manner through epigenetic modifications on the X chromosome, mainly failure of X inactivation. To test our hypothesis, we used the obese BPH/5 female mouse that spontaneously exhibits late-gestational hypertension, fetal growth restriction, and excessive gestational weight gain. BPH/5 offspring have sexually dimorphic cardiometabolic phenotypes with females being hyperphagic, obese, and hypertensive, while males are only hypertensive.

Methods: BPH/5 dams were pair-fed (PF) to C57 control dams beginning at conception. Male and female BPH/5 offspring were fed an ad libitum (lib) diet until investigated in adulthood. Continuous blood pressure was measured by radiotelemetry and tissues collected for morphometric and genomic analyses. Whole genome bisulfite sequencing from white adipose tissue (WAT) was performed.

Results: BPH/5 adult females have increased markers of obesity compared to male littermates that is associated with hypermethylation of androgen receptor on the X chromosome. Although X inactivation, as measured by Xist, was comparable to control mice. Adult BPH/5 female offspring had reduced visceral WAT and lower central blood pressure after pair-feeding BPH/5 dams.

Conclusions: Reduction in the maternal obesogenic environment may play a role in BPH/5 sex-dependent offspring differences via epigenetic modifications of the X chromosome. Future studies are needed to understand the transgenerational methylation of cardiometabolic genes in PE offspring to prevent the lifecycle of disease associated with obesity.

About the Presenter

Dr. Jenny Sones is an associate professor of equine reproduction at the Colorado State University College of Veterinary Medicine and Biomedical Sciences. She earned both a B.S. and a D.V.M. from Louisiana State University in 2004 and 2008, respectively. Following a year of private practice at Delta Equine Center (Vinton, Louisiana), Dr. Sones pursued advanced training in reproductive physiology as a Ph.D. student and resident in reproductive medicine at Cornell University (2010–2015). Board certified by the American College of Theriogenologists in 2016, Dr. Sones served on the faculty of the Louisiana State University School of Veterinary Medicine from 2015 to 2023. Her primary research interest focuses on maternal risk factors leading to preeclampsia (pregnancy-induced hypertension) and associated cardiometabolic outcomes in offspring using a genetic mouse model. Dr. Sones has established an independent translational biomedical research program investigating pregnancy maintenance mechanisms in the horse and mouse models. This program is funded by the Theriogenology Foundation, National Academy of Medicine, NIH, COBRE, and a COBRE administrative supplement from ORWH.

Mechanism of tumor suppressor function of progesterone receptor in breast cancer

Motoki Takaku, Ph.D.
Assistant Professor, Department of Biomedical Sciences
University of North Dakota

Publication: Saotome, M., Poduval, D. B., Nair, R., Cooper, M., & Takaku, M. (2022). GATA3 truncation mutants alter EMT related gene expression via partial motif recognition in luminal breast cancer cells. *Frontiers in Genetics,* 13. https://doi.org/10.3389/fgene.2022.820532

Affiliation: University of North Dakota School of Medicine and Health Sciences, Department of Biomedical Sciences.
Funding: UND Genomics Core, ND-ACES (NSF EPSCoR), NIGMS COBRE, Admin Supplements on Women's Health

Abstract

Background: Breast cancer development is closely linked to the activity of hormone receptors, including estrogen receptors (ER) and progesterone receptors (PR). While ER's role in breast cancer and its targeting therapies are well-understood and established in clinical practice, PR's function remains underexplored, despite its presence in approximately 70% of breast cancers and the promising inhibitory effects of progesterone treatment. This knowledge gap, combined with the dual role of progesterone in both breast cancer progression and risk, underscores the urgent need for more detailed investigations into PR mechanisms.

Methods: Preliminary data suggest that PR regulates key miRNAs involved in cell cycle control, possibly through chromatin binding to the miRNA coding regions. We designed a CRISPR knockout screening to explore the roles of these progesterone-regulated miRNAs. In this process, luminal T47D cells were exposed to progesterone for 1 month, and resistant clones were then collected for downstream analysis.

Results: The CRISPR screening revealed that gRNAs targeting specific miRNAs were enriched following progesterone exposure. These miRNAs were up-regulated by progesterone treatment, and PR binding in proximity to these miRNAs was observed. Depletion of these miRNAs resulted in T47D cells exhibiting resistance to progesterone treatment. Notably, the expression of miR-30a correlates with PR expression in clinical breast cancer gene expression data.

Conclusions: This study identified specific miRNAs regulated by progesterone and demonstrated that their combined action is necessary to inhibit luminal breast cancer cell growth. These findings provide new insights into how progesterone-activated PR may inhibit tumor growth in breast cancer.

About the Presenter

Dr. Motoki Takaku is an assistant professor in the Department of Biomedical Sciences at the University of North Dakota. He earned his Ph.D. in biochemistry from Waseda University, conducting research on DNA repair under the supervision of Dr. Hitoshi Kurumizaka. Following this, he completed postdoctoral training in the laboratory of Dr. Paul Wade at the National Institute of Environmental Health Sciences (NIEHS), where he focused on gene regulation in breast cancer. He established his laboratory in 2019 and served as a project leader for the Epigenomics of Development and Disease COBRE Phase 2. He has successfully graduated from the COBRE program after securing multiple grants, including R01 and American Cancer Society Research Scholar Grant. His research primarily focuses on the roles of chromatin and its regulators in breast cancer, utilizing advanced genomics and machine learning techniques.

My Best Alaskan Life

Allex Mahanna, M.P.H., Project Manager
Lauren Lessard, Ph.D., Assistant Professor
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Publication: Lessard, L., Jessen, C., Buckingham, S. L., Russell, R., Morgan, S. A., & Baker, J. (2024). My Best Alaskan Life: Addressing Adolescent Mental and Reproductive Health in Alaska. Health Promotion Practice, 15248399231221769.

Affiliations: University of Alaska, Anchorage; Institute for Circumpolar Health Studies; INBRE and CTR-IN Affiliations

Abstract: Alaskan youth lead the nation in gonorrhea and chlamydia infection rates. Contraceptives are inconsistently used, with 46% of youth not using condoms during their last sexual intercourse and 15% not using any pregnancy prevention method. Alaskan youth also experience disproportionately high rates of suicidality and hopelessness, and poor mental health is related to high risk sexual behaviors. The My Best Alaskan Life (MBAL) digital tool is a preventive approach to support young adult health practices, designed by and for Alaskan youth. This presentation will explore benefits of using the RLP in supporting youth sexual and mental health decision making. We will also provide an overview of MBAL's culturally-specific modules and evidence-supported materials. Finally, we will offer insights on effective community and youth engagement in co-designing interventions, presenting strategies that researchers can use in their own co-developed youth-driven preventive interventions.

About the Presenters

Ms. Allex Mahanna graduated from the University of Iowa with a B.S. in global health studies and a B.A. in ethics in public policy. She is an M.P.H. candidate at the University of Alaska, Anchorage (UAA). Her background includes involvement in mixed methods research in mental health, as well as hands-on experience in direct service work and public health education. Over the past 2 years, she has conducted research with diverse groups, including young adults aged 14–26, older adults over 60, perinatal populations, LGBTQIA2S+, and gender expansive communities. This includes work with the University of Massachusetts Chan Medical School, where she served as a graduate epidemiology intern through the Association of Maternal and Child Health's Graduate Student Epidemiology Program. Additionally, Ms. Mahanna played a pivotal role in supporting the grant writing and tracking process for a free medical clinic in Illinois, helping to secure funds exceeding $3.5 million, which directly contributed to improving the health outcomes of uninsured and underserved chronically ill populations. As the current project manager for the MBAL project, she supports host site coordination and recruitment efforts, the youth and community advisory boards, data analysis, and result communication. She has also

assisted in the development of an R15 grant application aimed at providing additional data on the effectiveness of MBAL in young adult Alaskan communities.

Dr. Lauren Lessard is an assistant professor of health sciences and a maternal and child epidemiologist at the Institute for Circumpolar Health Studies. She has extensive experience developing research protocol and interventions addressing reproductive health disparities and inequities. Her current projects include a Patient-Centered Outcomes Research Institute (PCORI)-funded comparative effectiveness study evaluating enhanced prenatal care systems, Project EMBRACE. Dr. Lessard's previous projects focused on coordinating with practitioners and patients to address key maternal health issues including maternal mental health, obesity and contraception use, racial and cultural humility in clinic settings, adolescent preconception health, and comorbidities associated with preterm birth. Prior to her role at UAA, she served as the research director for the Fresno County Preterm Birth Initiative at the CSU Fresno and Research Scientist for the Central Valley Health Policy Institute. Dr. Lessard completed her Ph.D. in public health at the University of California, Los Angeles and her M.P.H. in maternal and child health at the University of California, Berkeley. Prior to completing graduate school, she was a Peace Corps Volunteer in Suriname, South America, and completed her B.A. political and community science at the University of California, Santa Cruz.

Microplastic accumulation in placentas from adverse pregnancy outcomes

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Abstract

Background: Microplastic (MP) fragments have been found in a variety of human tissues including the human placenta. The impact that plastic compounds have on maternal-fetal physiology, however, is poorly understood. With the exponential rise in plastic production, human exposure to MP is rising, emphasizing the need to evaluate the implications that MPs may play in affecting pregnancy and women's health.

Methods: Control (n=50), Fetal Growth Restricted (FGR/n=10), Preeclampsia (PE/n=9) and Macrosomia (MS/n=10) banked placentas (15g) were retrieved from the Hawaii Biospecimen Repository (NIMHD, RMATRIX #U5MD007584), washed with pre-filtered water in a plastic-free environment, placed into glass containers with glass lids, and treated with pre-filtered 10% KOH solution (1:8, w/v) for 7 days at room temperature to digest all organic biological material. Digested samples were filtered using a 1.6µm pore glass fiber filter (Whatman GF/A) to collect possible MP debris for analysis. Procedure controls were processed in parallel as contamination control (water and air-exposed glass filter, KOH solution, effluent collected from placenta storage tubes, and placenta collection plastic containers) to account for any baseline MP exposure. MP-like particles were characterized using Raman spectroscopy, and assigned spectra were determined using KnowItAll Spectroscopy software and SLOPP and SLOPPe libraries. The topography of selected MP was assessed by Scanning Electron Microscopy (EDS).

Results: Microplastic/polymer/dye particles were found in 30 out of 50 Control placentas; 5 out of 10 FGR; 5 out of 11 Macrosomia; 7 out of 9 with Preeclampsia. A total of 114 different polymer spectra were acquired. All procedure control

spectral contaminants were excluded from the spectral analysis. MP size ranged from 1µm to 40µm. The most abundant MP components were polypropylene, acrylonitrile, and polyester. Multiple dyes were also identified including Cromopthal Blue, Phthalocyanine blue Yellow 82, Yellow 83, Red 170, and Red 179. Traditional plasticizers and unidentified polymers and dyes were also detected.

Conclusions: Preliminary data suggests a possible association between MP accumulation and polymer composition with adverse pregnancy outcomes, including elevated number of polypropylene MPs in placentas from macrosomic pregnancies, and elevated MPs containing yellow polymeric dye found in samples from FGR pregnancies when compared to controls. SEM-EDS confirmed the chemical composition and ultrastructure of the most commonly found MPs. The pathophysiology of how the physical characteristics of MPs and/or chemical composition can lead to an adverse pregnancy outcome have yet to be elucidated.

About the Presenter

After receiving a B.S. from the Honors Program in Medical Education at Northwestern University, Dr. Men-Jean Lee earned her medical degree from the Northwestern University School of Medicine. She completed her residency in obstetrics and gynecology at Prentice Women's Hospital at the McGaw Medical Center Medical Center of Northwestern University, and pursued fellowship training in maternal-fetal medicine at Strong Memorial Hospital at the University of Rochester. Dr. Lee has served on the faculties of New York University (NYU), Yale University, Indiana University, and the Mount Sinai School of Medicine. She was a recipient of Reproductive Scientist Development Program-NICHD K-12 award to study in the Department of Microbiology at NYU, the transcriptional regulation of the glucocorticoid receptor in the human placenta. She is currently a co-investigator in a COBRE supplement with Dr. Johann Urschitz and Dr. Steve Ward at the Institute for Biogenesis Research to study the impact of microplastics in human placentas from births in Native Hawaiian and Pacific Islander populations. Dr. Lee's special research interests include maternal stress during pregnancy, glucocorticoid effects on fetal development, social determinants of health and disease, epigenetics, and placental biology. She is the Kosasa Endowed Professor and associate chair for research and innovation in the Department of Obstetrics and Gynecology at the University of Hawaii, John A. Burns School of Medicine. As a maternal-fetal medicine specialist, she continues to deliver babies, and as the medical director for the Fetal Diagnostic Center at Kapiolani Medical Center for Women and Children, Dr. Lee provides prenatal diagnosis, ultrasound services, and perinatal consultations for the pregnant women of Hawaii and the Pacific Islands.

ADDITIONAL ABSTRACTS

Fibroblast MMP14 overexpression and cardiac function in pregnant and postpartum mice

Holly LaVoie, Ph.D.
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Authors: Holly LaVoie, Ridha Fatima, Emily Walliser, Aiden Maragh, Jessica Simpson

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Abstract

Background: Physiological remodeling of the heart occurs during pregnancy and reverses postpartum. Elevated Matrix metallopeptidase 14 (MMP14) is associated with pathological remodeling of the heart. We aimed to determine if overexpression of MMP14 in mice would alter maternal cardiac function and extracellular matrix (ECM) parameters during pregnancy and postpartum.

Methods: We utilized mice expressing a human MMP14 (hMMP14) transgene under control of the murine Col1a2 promoter which expresses predominantly in fibroblasts. Wildtype and hMMP14 adult female mice were mated, underwent serial echocardiography, and were euthanized for tissue collection at day 17 of pregnancy or postpartum day 49. Age-matched virgins were also analyzed.

Results: Heart weight normalized for tibia length was highest in pregnant mice of both genotypes. In both genotypes, stroke volumes (SVs) at ppd 2, 7, 14, and 21 were higher than their respective virgin levels. In addition, in hMMP14 mice at ppd28 SV was higher than starting virgin levels. Investigation of mRNAs for ECM molecules found differences in reproductive status and/or genotype in specific TIMP and collagen genes. Most changes were associated with pregnancy rather than genotype.

Conclusions: Overall, there were few differences in cardiac function, ECM proteins and their mRNAs between genotypes, indicating adaptation to MMP14 level differences. The largest impact on cardiac function, ECM mRNA and protein expression was pregnancy. In addition, hyperactivity was observed in about 20% of females and an increased incidence of grossly abnormal ovaries, findings we are investigating further. Acknowledgments: Dr. Frank Spinale for mice and funding from SC INBRE P20GM103499.

Molecular dynamics of the human papillomavirus to identify novel drug targets

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Affiliation: COBRE Discovery of Chemical Probes and Therapeutic Leads at University of Delaware

Abstract

Background: Cervical cancer, predominantly caused by the human papillomavirus (HPV), remains a significant global health issue despite the availability of vaccines and screening programs. The HPV capsid—a protein shell that encases the virus, which is also the major component of vaccines—represents a promising drug target.

Methods: We employ all-atom molecular dynamics (MD) simulations to characterize the intact HPV type 16 capsid. These simulations reveal the detailed motion and transient structural features of that capsid that are not apparent in experimentally derived structures—such as cryptic pockets that may represent novel drug binding sites.

Results: Using integrative modeling, we have constructed a complete model of the full-length, intact HPV capsid at atomistic resolution. We have obtained an allocation on the National Science Foundation's leadership-class supercomputer FRONTERA and are running the world's first all-atom MD simulation of the HPV capsid within a realistic explicit solvent environment. This simulation encompasses over 16 million atoms and represents the largest simulation of an icosahedral virus capsid performed to date.

Conclusions: The detailed biophysical characterization provided by our simulations opens new avenues for developing HPV inhibitors and enhancing vaccine design. These insights will advance our understanding of HPV capsid function during infection and assist in identifying novel anti-capsid drug targets.

OBGYN virtual cases utilizing social determinants to enhance clinical reasoning

Qingsong Zhao, Ph.D.
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Abstract

Introduction: Addressing health equity challenges stemming from social determinants of health is crucial in obstetrics and gynecology education.

Hypothesis/Study Objective: This pilot project aimed to enhance obstetrics and gynecology foundational knowledge and clinical reasoning among medical and nursing students during their clinical training years. Additionally, its goal was to raise awareness regarding social determinants of health and microaggressions contributing to health disparities in this context.

Methods and Findings: The project developed a virtual case repository to target foundational knowledge and clinical reasoning in obstetrics and gynecology education. An e-learning platform, termed e-ObGyn, was created based on this repository. Assessment involved pre- and post-test case evaluations and feedback from students, including clinical knowledge, health disparity content, and platform usability. A total of 26 participants, 19 in physician assistant (PA) students and 7 in physical therapy (PT) students, engaged with the platform. The surveys were comprised of 25 questions across four categories. Our analysis revealed significant improvements: 87.5% of the participants acknowledged the importance of healthcare recommendations, education level, and socioeconomic status in healthcare delivery. 100% of the participants gained confidence in understanding and discussing social determinants of health (SDoH) domains. 100% of the participants felt more confident in understanding and discussing SDoH topics with patients.

Discussion/Conclusions: The study demonstrated significant differences in participants' pre- and post-test scores, indicating the positive impact of case-based learning on social determinants in clinical reasoning.

Targeting STAT3 in ovarian cancer

Sarah Walker, Ph.D.
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Abstract

Background: Ovarian cancer metastasis remains a major health issue for women. Ovarian cancer metastasizes when clusters of cells from the primary tumor interact with the mesothelial layer lining the peritoneum, clearing the mesothelial cells, and invading underlying tissue. We previously identified STAT3 as important for mesothelial clearance. We sought to identify drugs that could inhibit STAT3, hypothesizing this could reduce mesothelial clearance and potentially treat or prevent metastatic disease. We previously identified several statins as potential inhibitors of STAT3 using CLUE. Recognizing that several studies demonstrated reduced ovarian cancer incidence in patients that took statins, we wanted to determine the effects of statins on cell survival and mesothelial clearance. As endometriosis shares some similarity with ovarian cancer, we also wanted to determine if endometriosis cells could undergo mesothelial clearance and if statins could be effective in modulating endometriosis cells.

Methods: We utilized the mesothelial clearance assay to assess the ability of ovarian and endometriosis spheroids to clear the mesothelial cells.

Results: We found that statins reduce the viability of both ovarian cancer cells and endometriosis cells. In addition, we have found that statins reduce the ability of ovarian cancer cells to clear mesothelial cells. Moreover, we have shown for the first time that endometriosis spheroids also clear mesothelial cells and STAT3 appears to play a role. Importantly, treatment with statins significantly reduces mesothelial clearance by endometriosis cells.

Conclusions: Our work suggests that statins may be beneficial as prevention or treatment for ovarian cancer and endometriosis.

Female Patient Outcomes for Inflammatory Bowel Disease Improve Following Programmed Physician Interactions during Infusion Treatment: "Symptomatic Review of Biologic Therapy in IBD" (STABILITY)

Urska Cvek, ScD
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Abstract

Inflammatory bowel disease (IBD) is a chronic condition characterized by gastrointestinal tract inflammation often with extra intestinal manifestations and co-morbidities. IBD is often treated with 'biologics' given intravenously at infusion clinics with periodic monitoring (colonoscopies, labs and/or abdominal imaging) scheduled at separate medical appointments.

At LSUHSC-S, IBD patients who received biologic infusions did not routinely meet with gastrointestinal (GI) physicians unless requested by the patient, or unless an infusion nurse. Disease progression in these patients was less well monitored, and valuable changes in their medication dosing, treatment frequency, or therapy adjustment were often missed.

Meetings with GI physicians were instituted at the infusion clinic and named STABILITY (Symptomatic Review of Biologic Therapy). STABILITY patients were given anonymous surveys during their infusions to measure understanding of their disease, progression of their symptoms, and whether they would want to continue seeing a GI physician during their infusions. Clinical disease severity, colonoscopy evaluations, and levels of inflammatory biomarkers were measured in 110 patients before and after STABILITY using a paired two-tailed t-test.

In females with IBD, disease severity and hospitalizations were significantly reduced ($p=0.0001$ and 0.0072 respectively). Disease severity was significantly reduced in UC females ($p=0.0379$) and CD females ($p= 0.0003$) and hospitalizations in CD females were also significantly reduced ($p=0.013$). Data analysis revealed reductions in inflammatory biomarker levels in

female CD and UC patients although this did not reach statistical significance. STABILITY protocols have an important place in maintaining patient health in IBD and are a highly cost-effective strategy to improve patient outcomes.

Mechanical regulation of cisplatin-DNA adduct repair in mesenchymal stem cells

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Abstract

Background: First-line platinum-based chemotherapies, which are crucial for treatment of breast, ovarian, cervical, and testicular cancers, work through the formation of bulky DNA adducts. However, off-target DNA damage in healthy cells leads to debilitating short- and long-term side effects including bone wasting. Exercise can decrease side effects; however, cancer related fatigue poses an insurmountable challenge. We hypothesize that passive mechanical stimulation can reduce side effects by preferentially enhancing the DNA damage response in healthy cells, but not in cancer cells.

Methods: We applied mechanical stimulation in the form of *Low Intensity Vibration* (LIV), an exercise mimetic that requires intact *Linker of Nucleoskeleton and Cytoskeleton* (LINC) complex to transduce signals into the nucleus. Critically, endogenous LINC complex downregulation is associated with breast cancer progression and poorer prognosis. We examined whether LIV alters the kinetics of cisplatin-induced DNA adduct repair in cultured Mesenchymal Stem Cells (MSC) with intact or disrupted LINC complex.

Results: We show that LINC-mediated mechanotransduction is critical for efficient Nucleotide Excision Repair of bulky DNA adducts. DNA damage removal increases by 20% in LIV treated MSCs compared to non-vibrated samples at 24 hours ($P<0.005$). However, LINC complex disruption significantly reduced removal of cisplatin-DNA adducts ($P<0.001$).

Conclusions: These findings suggest a novel interaction between mechanical stimulation, the DNA damage response, and the LINC complex. Furthermore, we suggest that LINC-mediated mechanoregulation of the DNA damage response may lead to novel nonpharmacological therapeutic approaches to combat deleterious musculoskeletal conditions associated with off-target effects during anti-cancer treatment.