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Technology and Innovation in Women's Health Research

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DIRECTOR'S CORNER

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We are living in a golden age of biology and technology. Innovations in tissue engineering, biomedical imaging, computational science, and molecular and cellular biology are transforming our ability to understand complex biological mechanisms and pathways and to study interactions among human cells, tissues, and substrates at the molecular level.

Major investments by the National Institutes of Health over the past decades have spurred advances in in vitro bioengineering tools that enable the use of human cells and tissues for preclinical testing. These advances have the potential to reduce costs and to accelerate the development, testing, and clinical use of novel therapeutics. This issue of In Focus *describes how these advances are accelerating research on several conditions that solely or predominantly affect women, including gynecological cancers and endometriosis, and revealing promising new avenues for treatment.*

The issue also highlights how advances in biomedical imaging are transforming maternal health care through the development of new clinical algorithms and medical devices that can improve the detection of intrauterine growth restriction, postpartum hemorrhage, and preterm labor.

For our Women in Science interview, we hear from Shelly Peyton, Ph.D., who serves as a Professor of Biomedical Engineering and a Professor of Chemical and Biological Engineering at Tufts University. She shares her experiences applying her expertise in chemical engineering and biomaterials to the study of breast cancer and in spearheading efforts to increase diversity among engineering students.

Finally, this issue spotlights several recent ORWH events, research articles relevant to women's health, and the launch of the new NIH Discover Women's Health Research (DiscoverWHR), a centralized resource for NIH information on women's health.

We hope you will share this exciting issue of In Focus *with your colleagues. You* can subscribe to In Focus *online.*

Innovations in Research on the Health of Women

Bioengineering Is Transforming Cancer Research

Researchers are now using groundbreaking innovations in bioengineering to develop complex 3-dimensional (3D) models of human tissues, organs, and organ systems—giving researchers a once unfathomable ability to probe human biological systems in real time.

One area being transformed is cancer research, particularly research on what is known as the cancer microenvironment—the cells, tissues, fluids, and substrates that surround and interact with cancer cells. Using bioengineering, researchers can now study how cancer cells interact with their environment, including immune system cells, cellular support structures (e.g., the extracellular matrix [ECM]), fluids, and blood and lymphatic vessels.

> The extracellular matrix, or ECM, consists of the proteins and other molecules that surround, support, and provide structure to cells and tissues in the body. This matrix plays essential roles in cell growth, movement, and other cellular functions. The ECM can also play a role in the growth and spread of cancer cells.

Because researchers can maintain these models for weeks to months in the laboratory, they can study how the complex cell-to-cell and cell-to-ECM interactions involved in cancer's growth and spread evolve over time. By improving our ability to understand and potentially target and disrupt these interactions, this research is opening new therapeutic frontiers in cancer treatment.

Studying Ovarian Cancer and Immune System Interactions

Nearly 20,000 women in the United States receive a diagnosis of ovarian cancer each year, and only half of them will survive five years after diagnosis.[1] Ovarian cancer is particularly lethal because it frequently metastasizes (spreads) to additional sites within the abdomen, including the liver and colon.[2,3]

Complex interactions between immune cells and ovarian cells contribute to ovarian cancers' deadly spread, says Shreya Raghavan, Ph.D., an Assistant Professor of Biomedical Engineering at Texas A&M University, who studies the ovarian cancer tumor microenvironment.

Shreya Raghavan, Ph.D., Texas A&M University

Because of the ovaries' role in reproduction, they are already an immune-privileged environment, explains Dr. Raghavan. It is relatively easy for cancer cells in this environment to evade immune detection and destruction.

As an ovarian tumor grows, it sheds cancer cells into the fluid-filled abdominal cavity. As these cells circulate in the abdominal cavity, they form spherical shaped clusters of cancer cells that aid in their survival. These clusters then transition from focusing on survival and immune evasion to focusing on colonization of new sites (i.e., metastatic spread), making this a potentially critical period for intervention.

As they circulate within the abdominal fluid, the spherical clusters interact with a type of immune cell known as macrophages. These interactions gradually reprogram the macrophages from cells that would normally help detect and kill cancerous cells to cancer enablers, says Dr. Raghavan. The reprogrammed macrophages release chemicals that urge the cancer cells to become more "stemlike" (i.e., more like stem cells), allowing them to more easily evade other immune cells.[4] Stem-like cancer cells have longer lifespans, have an enhanced capacity for self-renewal, and are relatively resistant to chemotherapies.[5] The reprogrammed macrophages also pave the way for metastases, by migrating to other sites such as the liver, where they actively create a pre-metastatic niche and then signal to the cancer cells to home to that niche, says Dr. Raghavan.

To simulate and study these macrophage–ovarian cancer cell interactions in the laboratory, Dr. Raghavan designed a hanging drop array that creates the spherical clusters of ovarian cancer cells, reflecting their natural 3D architecture.

Although hanging drop arrays have been used in research for decades, the older techniques were very fragile and cumbersome to work with, says Dr. Raghavan. If a laboratory technician so much as sneezed while holding one of these older arrays, weeks of work could be lost. The older arrays also required relatively large numbers of cancer cells. By contrast, Dr. Raghavan's hanging drop array can create a cancer cell cluster from as few as 10 cancer cells—a difference that enables the study of individual patients' cancers as well as of rare types of cancer cells, such as stem-like ovarian cancer cells.

Using these arrays, Dr. Raghavan has discovered several signaling pathways involved in transforming macrophages from cancer killers to cancer enablers and is now testing whether different drugs can disrupt this process. Such drugs would take a different, and potentially complementary approach, than current, more active immunotherapies, she notes. Current immunotherapies aim to enhance existing but insufficient immune attacks on cancer cells, whereas these drugs would instead aim to prevent macrophages from enabling ovarian cancer growth and spread.[6]

Developing a Synthetic Bone Marrow to Study Dormant Breast Cancer Cells

One in eight women living in the United States (U.S.) will develop breast cancer, and although the 5-year survival rate for early-stage breast cancer is excellent, exceeding 99%, a substantial fraction of women treated for early-stage breast cancer eventually experience a relapse, sometimes years after their initial treatment.[7,8] These recurrences frequently arise from so-called dormant breast cancer cells—cells from the original tumor that spread to other organs and then remained dormant for months to decades.[9]

Shelly Peyton, Ph.D., Tufts University

Dormant breast cancer cells are not actively dividing and growing, and thus are not susceptible to chemotherapy. These cells can remain inactive for decades, but then suddenly reawaken and begin to divide and spread very aggressively, says Shelly Peyton, Ph.D., Professor and Chair of Biomedical Engineering at Tufts University. Once they awaken, she adds, these cancer cells are highly resistant to treatment.

Dormant breast cancer cells are most often found in the bone marrow, Dr. Peyton says, suggesting that something about the bone marrow environment is conducive to dormancy, and further that specific changes in this environment may provoke their reawakening.

Studying dormant breast cancer cells in animal models is difficult, because imaging does not penetrate the bone and because many of the proteins in the bone marrow cannot be studied through gene editing. Changes to these proteins are lethal early in development.

Thus, to study how the environment of the bone marrow affects the dormancy and reawakening of these dormant cells, Dr. Peyton has developed a laboratory-based 3D model of dormant human-derived breast cancer cells embedded in synthetic bone marrow. "By combining synthetic polymers with proteins found in real bone marrow, we can mimic all the proteins a metastatic breast cancer cell would interact with in that environment as well as match the softness of the environment, which is incredibly soft, almost a liquid," she explains. Matching the normal softness of bone marrow

is particularly important, because research has shown that stiffening of tissues can promote cancer growth and spread.[10]

Using this model, Dr. Peyton is studying how changing bone marrow proteins and stiffness affects dormant breast cancer cells, as well as how the cancer cells alter the marrow during dormancy and reawakening. She discovered that within the bone marrow, dormant breast cancer cells tend to cloak themselves in a mat of fibronectin, a scaffolding protein abundant in the ECM that facilitates cell to ECM adhesion.[11] After reawakening, the cells must dissolve this mat before they can proliferate.[11] These findings open the door to new therapies that target the mechanisms that enable reawakening and the dissolution of the mat. "If we can find therapies that prevent these cells from reawakening before the person dies of natural causes, that is a great outcome," she says.

Dr. Peyton also is using her bone marrow model to screen new therapies and to study cancer cells derived from specific patients. "These biomaterial models allow rapid fire plug and play," she says. "You can make a 96 well plate of synthetic bone marrows and use liquid handling robotics for high-throughput screening." These features enable rapid testing of different therapeutics. Longer term, oncologists may be able to use similar models to test the effectiveness of different drugs for individual patients prior to initiating treatment.

Investigating How Fluid Flow Contributes to Breast Cancer's Spread

One of the first places breast cancer spreads is to nearby lymph nodes. Lymph nodes are bean-sized structures that drain lymphatic vessels and filter the interstitial fluid—the fluid that bathes our bodies' cells.

Jennifer M. Munson, Ph.D., Fralin Biomedical Research Institute; Virginia Tech

As it flows through tissues and into lymphatic vessels, interstitial fluid exerts mechanical forces on the surrounding cells, including on tumor cells. These forces alter tumor cells' gene expression and behavior and contribute to the spread into the lymph nodes, says Jennifer M. Munson, Ph.D., Professor at Virginia Tech's Fralin Biomedical Research Institute at VTC, Director of the institute's Cancer Research Center in Roanoke, and Professor of Biomedical Engineering and Mechanics with Virginia Tech's College of Engineering.

To study the biological mechanisms by which fluid flow affects cancer cell growth and spread, Dr. Munson builds 3D model systems using multiple types of human-derived cells, including support cells, tumor cells, immune cells, and cells that line the lymphatic vessels. These models aim to recapitulate the tissue and fluid environment that surrounds a breast tumor. To ensure that these models accurately reflect how fluid flows within the tumor environment, she has developed a tracer-based method to study fluid flow dynamically in mice and humans.

"These systems allow us to add and remove different components to test how each component potentially contributes to invasion into the lymphatic system, which is something we want to avoid, because once these cells enter the lymphatic system then they can enter the bloodstream and spread to places like the lung or the brain or the liver, where they are much, much more difficult to treat," explains Dr. Munson.

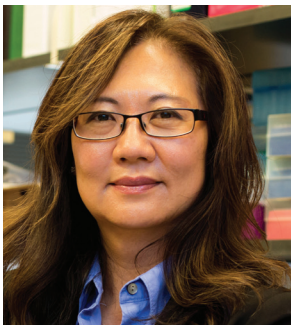
Using these systems, Dr. Munson discovered that low doses of platinum-based chemotherapy commonly used to treat breast cancer, can promote the enlargement, sprouting, and proliferation of lymphatic vessels (i.e., lymphangiogenesis) throughout the body, in both healthy and cancerous tissues. In cancer patients, lymphangiogenesis at primary tumor sites or metastatic sites corresponds to increased cancer growth, metastasis, and poor prognosis.[12] She also has shown that antibody-based therapies that block the VEGFR3 cellular receptor on the cells lining the lymphatic vessels can prevent this lymphangiogenesis.[12]

Dr. Munson is now involved in multiple ongoing collaborations using her methods for studying fluid flow. The collaborations are studying fluid flow in a wide range of conditions, including pregnancy, Alzheimer's disease, brain cancer, lymphedema (a type of swelling that may occur after chemotherapy), and lipedema (a condition characterized by excess fluid and fatty tissue in the legs and arms that almost exclusively affects women). Longer term, she hopes to use her fluid flow models to study the factors that determine whether different individuals' cancers respond to specific chemotherapies or immunotherapies.

Probing the Biological Mechanisms of Risk Factors for Endometrial Cancer

Endometrial cancer begins in the endometrium, the tissue lining the uterus.[13] It is the most common gynecological cancer in developed countries and the sixth cause of cancer deaths among women.[14]

Over the past several decades, the incidence of endometrial cancer has risen in the U.S. and many other countries. Rising rates of obesity, a major risk factor for endometrial cancer, are thought to be a key driver of this trend.[14] More than half of the endometrial cancers in the U.S. are thought to be attributable to excess body fat, and women with endometrial cancer who are obese have a worse prognosis.[15]



Ji-Yong Julie Kim, Ph.D., Northwestern University

To study the role of excess body fat in endometrial cancer, Ji-Yong Julie Kim, Ph.D., Susy Y. Hung Professor of Obstetrics and Gynecology and Co-director of the Center for Reproductive Science at Northwestern University, has developed 3D tissue models, or organoids, of the endometrium grown from human cells. Although endometrial tissue was once notoriously difficult to maintain in the laboratory, Dr. Kim has overcome this hurdle by continually replenishing the endometrial organoids' media using a microfluidic plate (a cell culture plate consisting of multiple wells connected by channels and attached to a pump).

Dr. Kim is using these endometrial organoids and microfluidic plates to investigate the biological mechanisms by which excess body fat increases the risk for endometrial cancer. In a series of studies, she co-cultured these endometrial organoids with adipose (fatty) tissue and then exposed the organoids to reproductive hormones. She then assessed gene expression, protein expression, and markers of DNA damage in the endometrial cells. She found that, in high adiposity conditions, endometrial epithelial cells downregulated the expression of family of genes known as metallothionein genes.[16] Progesterone normally increases the expression of metallothionein genes, which are involved in the secretory (shedding) phase of the menstrual cycle. These results suggest that excess body fat may increase the risk for endometrial cancer by decreasing endometrial epithelial cells' responsiveness to progesterone.[16] Prolonged exposure to estrogen without the opposing action of progesterone is a well-established endometrial cancer risk factor.[17] Dr. Kim is now expanding on these findings by studying how exposure to fatty tissue affects the behavior of endometrial cancer cells.

Improving Diagnosis and Treatments for Endometriosis

An estimated 1 in 10 reproductive age women have endometriosis, a condition in which endometrial-like tissue grows outside the uterus, spreading to the ovaries, fallopian tubes, and other sites in the pelvic cavity, where it can cause debilitating pain, excessive bleeding during menstruation, and infertility.[18]

Although endometriosis is common, it is underdiagnosed, and women with symptoms often wait years before receiving a diagnosis.[19] Multiple factors contribute to these diagnostic delays: Women and their providers may lack awareness of endometriosis and its symptoms; the symptoms can be nonspecific; and conclusive diagnosis requires laparoscopy, an invasive procedure.

Improving Diagnosis of Endometriosis by Analyzing Menstrual Blood

Ridhi Tariyal, M.B.A., S.M., NextGen Jane

Fundamentally, providers lack noninvasive tools for diagnosing endometriosis because we do not understand its molecular characteristics, says Ridhi Tariyal, M.B.A., S.M., Chief Executive Officer and Co-founder of NextGen Jane, a startup focused on developing menstrual blood–based screening tools and diagnostics.

NextGen Jane is conducting several studies to determine whether molecular analyses of menstrual blood can screen for, and potentially diagnose, endometriosis. One of these studies is assessing whether testing menstrual blood can aid in the diagnosis of endometriosis in the context of infertility. Many women with endometriosis present at fertility clinics because they are struggling to become pregnant, so infertility is an especially important context in which to improve diagnosis and treatment, says Ms. Tariyal.

Menstrual blood has several advantages over blood obtained via a standard blood draw, she adds, such as greater accessibility. Menstrual blood samples can be obtained noninvasively at home, so women do not have to visit a clinic for collection. Women participating in NexGen Jane's studies are sent at-home collection kits that collect blood via tampons. Accessibility is especially important because of the increasing number of gynecological care deserts in the U.S., notes Ms. Tariyal.

A second advantage is that menstrual blood also contains cells specific to the endometrium not found in a standard blood draw, including endometrial cells and naturally occurring bacteria found in the uterus. These cells may provide a more precise picture of uterine and endometrial health.

A third advantage is that "menstrual blood provides a 28- to 30-day lagging indicator of total hormonal health," says Ms. Tariyal, "because coordinated changes in estrogen and progesterone dictate the endometrium's thickening and shedding over the course of the menstrual cycle."

NextGen Jane is storing and analyzing the menstrual blood samples it collects and is recording their molecular characteristics, such as gene expression and the presence of different types of bacteria. Using these data, NextGen Jane has identified a characteristic molecular signature predictive

of having endometriosis that may help inform a menstrual blood-based diagnostic.

NextGen Jane is also actively testing different treatments for endometriosis on these samples. Endometriosis has no cure, and most treatments are "blunt instruments" that involve surgery or drugs that affect fertility or induce menopause, says Ms. Tariyal. Even after surgery, the disease can recur.

Building In Vitro Tissue and Extracellular Matrix Models for Studying Endometriosis

Animal models have major limitations for preclinical testing of potential treatments for endometriosis, says Linda G. Griffith, Ph.D., the School of Engineering Professor of Teaching Innovation at the Massachusetts Institute of Technology. Mice, for example, do not naturally menstruate nor develop endometriosis. Thus, drugs that might work in people could still fail during preclinical testing in mice.

Linda G. Griffith, Ph.D., Massachusetts Institute of Technology

To overcome these limitations, Dr. Griffith developed complex, multi-system human-based tissue models of endometrial lesions, immune cells, and blood vessels to test new therapeutics for endometriosis. To sustain these tissues in the laboratory, Dr. Griffith has developed a hydrogel-based synthetic media that recapitulates the normal composition and stiffness of the endometrial environment. Epithelial and stromal endometrial cells grown in this media exhibit normal cell-to-cell interactions when exposed to hormonal fluctuations characteristic of a menstrual cycle. They also exhibit disordered cell-to-cell interactions in the presence of inflammation, as occurs in endometriosis.

As with all these innovations, the applications for this new media are broad. "The media does not interfere with cell-to-cell communications, making it a powerful tool for organoid research," says Dr. Griffith. She has been inundated with requests for the media from researchers studying liver, gut, pancreatic and other organoids, and is now working to make the media commercially available in 2025.

Biomedical Imaging-Based Advances in Maternal Health Research

Building Novel Devices for Predicting Preterm Birth and Detecting Postpartum Hemorrhage

During pregnancy, cervical tissue remodels to enable its eventual dilation to the 10 cm required for delivery. "Cervical tissue in the ninth month of pregnancy is a completely different material from the tissue at the beginning of pregnancy," says Christine O'Brien, Ph.D., Assistant Professor of Biomedical Engineering at Washington University in St. Louis. "At three months of pregnancy, the cervix would rip apart before dilating to anything close to 10 cm."

Christine O'Brien, Ph.D., Washington University in St. Louis

This remodeling opens the door to studying cervical changes during pregnancy with Raman spectroscopy, explains Dr. O'Brien. Raman spectroscopy is a technology that uses an optical probe to shine a beam of light into a material, such as the cervix, several millimeters to a centimeter into the tissue. The probe then measures the light reflected back to ascertain the material's molecular composition within that depth.

Clinicians typically assess changes in molecular composition of tissues via biopsy, says Dr. O'Brien, but during pregnancy, cervical biopsies are generally avoided, because they could disrupt the structural integrity of the cervix or introduce an infection. Raman spectroscopy offers an alternative, noninvasive method for obtaining a quantitative, objective measure of the cervical changes occurring throughout pregnancy.

O'Brien began her work in this area as a PhD student at Vanderbilt University under the mentorship of Dr. Anita Mahadevan-Jansen. To study the load-bearing cervical stroma tissue which lies below the superficial epithelial layer, Dr. O'Brien and her colleagues designed and fine-tuned a Raman probe that can sense biochemical composition several millimeters deep by incorporating a microlens design. This microlens design preferentially collects Raman-scattered light deep within a tissue.[20]

She then worked with clinicians to ensure that the device could be incorporated into their existing workflows. These discussions made clear that using a speculum for probe insertion and guidance would be unpleasant for patients and would lengthen visit time, a major drawback for busy clinicians. Dr. O'Brien therefore added a small video camera at the end of the probe to enable clinicians to assess cervical composition without using a speculum.[21] Using this image-guided system, Dr. O'Brien and her colleagues have found that as pregnancy and labor progresses, the amount of collagen per volume of tissue in the cervix decreases, and hemoglobin (an indicator of blood content) increases.[22,23]

Understanding the cervical changes that occur during pregnancy and labor has several potential benefits. One is an improved ability to predict preterm labor, a complication

affecting roughly 1 in every 10 births in the U.S. and the leading cause of disability and death among children under age 5.[24,25] Predicting preterm birth early could enable clinicians to administer corticosteroids prior to delivery to spur fetal lung development and to improve overall health outcomes for premature babies. Corticosteroids are most effective when administered 48 hours prior to delivery, says Dr. O'Brien. A second potential benefit is an enhanced understanding of which preterm deliveries result from cervical changes rather than from infections or other causes. Finally, data from these studies may improve the ability to monitor labor progress. Currently, labor progress is typically assessed by measuring cervical dilation via a bimanual exam (i.e., by how many fingers can be inserted into the cervix)—an imprecise and subjective approach.

In addition to her research on cervical changes, Dr. O'Brien is applying her expertise to prevent postpartum hemorrhage (rapid blood loss after delivery). The leading cause of maternal deaths worldwide, postpartum hemorrhage accounts for more than a quarter of global maternal deaths each year.[26]

When the uterus fails to contract after delivery, women can rapidly lose blood, at a rate of more than half a liter of blood a minute.[27] Thus, early detection and treatment of postpartum hemorrhage are vital for preventing severe complications. However, early signs of blood loss are challenging to detect. In response to rapid blood loss, the body releases adrenaline and constricts peripheral blood vessels to compensate for the reduction in blood volume. Changes in vital signs such as blood pressure, oxygenation, and heart rate are therefore relatively late indicators of hemorrhage. By the time these vital signs indicate blood loss, blood transfusions and surgical interventions are often required, says Dr. O'Brien, so clinicians instead frequently rely on visual assessments for early detection. Unfortunately, these visual assessments can be highly inaccurate, because some blood loss during labor is normal and because blood can pool inside the uterus.

To address these challenges, Dr. O'Brien has developed a wrist-worn wearable that monitors changes in peripheral blood flow in order to detect postpartum hemorrhage early. The wearable assesses peripheral blood flow using the laser speckle flow index, a light-based measure of blood perfusion. The wearable has shown considerable accuracy in predicting blood loss in a swine model of postpartum hemorrhage, and Dr. O'Brien is now testing it in people.[28,29]

Creating Digital Twins for Assessing Placental Health

Early in pregnancy, the fertilized egg develops a placenta. The villi of the developing placenta burrow into the uterine lining to connect to the maternal blood supply. The placenta is key for a healthy pregnancy, because it essentially functions as all the internal organs for the fetus during pregnancy, regulating waste removal and nutrient and oxygen transport and serving as the immune system interface between the mother and fetus, explains Michelle L. Oyen, Ph.D., Associate Professor of Biomedical Engineering at Wayne State University.

Michelle L. Oyen, Ph.D., Wayne State University

Problems with the placenta give rise to a host of pregnancy-related complications, including intrauterine growth restriction (IUGR). One of the more common complications of pregnancy, IUGR is associated with increased risk for stillbirth and neonatal health complications and death.[30]

In the U.S., IUGR is currently diagnosed when a fetus's estimated weight, as measured by ultrasound, is less than the 10th percentile for gestational age. (In some countries, the cut off is less than the 3rd percentile for gestational age.) A major drawback of this diagnostic criterion is that it confounds naturally small fetuses with those suffering from poor growth.

To improve the diagnoses of conditions such as IUGR, Dr. Oyen is developing a registry of "placenta digital twins." She is collecting ultrasounds of placentas in the second and third trimesters, from pregnancies with possible IUGR and healthy pregnancies. After delivery, she collects the placentas and subjects them to high-resolution imaging. She then applies machine learning-based and artificial intelligence (AI)-based techniques to assess placental structure, such as overall size, thickness of the terminal villi, and porosity. She uses these measurements to build digital twins representing both healthy placentas and dysfunctional placentas from pregnancies affected by IUGR.

Her goal is to use these digital twins to identify structural changes in the placenta that clinicians can use to diagnose IUGR. She is also collaborating on projects to use these data to identify risk for placental failure late in pregnancy, a major cause of stillbirths and labor inductions, and to study preeclampsia, a common and potentially deadly complication of pregnancy characterized by high blood pressure and protein in the urine (signifying kidney damage).

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Scientist Spotlight: An Interview with Shelly Peyton, Ph.D.

Shelly Peyton, Ph.D., Tufts University

Shelly Peyton, Ph.D., currently serves as a Professor and the Department Chair of Biomedical Engineering at Tufts University. Prior to joining Tufts University, she was an NIH Kirschstein Postdoctoral Fellow in the Biological Engineering Department at the Massachusetts Institute of Technology (MIT) and served as the Armstrong Professional Development and Provost in the Department of Chemical Engineering at the University of Massachusetts, Amherst. She was a Pew Biomedical Scholar and has received numerous honors for her work, including an NIH New Innovator Award and a National Science Foundation (NSF) Faculty Early Career Development Program grant. She received her bachelor's degree in chemical engineering from Northwestern University and her master's and doctoral degrees in chemical engineering from the University of California, Irvine.

Dr. Peyton's interdisciplinary research team draws on their expertise in biological, chemical, and engineering to build simplified human tissue models using synthetic biomaterials. Her laboratory is using these models to study metastatic breast cancer and traumatic brain injury, with a particular focus on how different cell types interact with the biochemical and biophysical cues from the extracellular matrix.

In addition to her considerable research achievements, Dr. Peyton is also a longstanding advocate for diversifying engineering and the biomedical sciences. She has co-directed an NSF Research Experiences for Undergraduates (REU) site and an NIH T32 Biotechnology Training Program and has served as the lead principal investigator for a Postbaccalaureate Research Education Program at the University of Massachusetts, Amherst, funded by the NIH National Institute of General Medical Sciences, which awarded one-year intensive internships to students from historically excluded groups in preparation for graduate school in the biomedical sciences. She also runs an NSF-funded program called Engineering the Cell, which awards summer internships in her laboratory to female high school students.

How would you describe your primary area of research?

My laboratory is really a biomaterials laboratory. My training is in materials chemistry and the synthesis of soft materials. When I was a post doc at MIT several years ago, I was working on using those materials for wound healing, particularly for bone defects, but lots of the people around me were working on cancer-related projects. They were focused on teasing out what is occurring inside the cell to cause it to respond or not respond to different therapies. As I talked to them, I realized this area presented a good opportunity for someone like me, on the biomaterial side of thing, to study what is occurring outside the cell. How are different environments causing cells to spread and metastasize or to be drug resistant? My laboratory is now applying biomaterials technologies to study breast and lung cancer, as well as traumatic brain injury.

What are some of the accomplishments you are proudest of?

That all my students go on to do amazing things. My laboratory trains students from a range of educational backgrounds, such as chemical engineers, biomedical engineers, and cell biologists. It is wonderful to see people with these different educational and racial and ethnic backgrounds who see the world in really different ways tackle these problems with different perspectives and then see them leave to work at places like startups, or Moderna or Pfizer and use their training from the lab to accomplish remarkable work.

What are some of the most significant barriers you have faced in your career?

I think it's challenging to work at interfaces. The excitement that stems from having a particular background and applying it to a new area is wonderful, but in practice it can be challenging to obtain funding for those projects.

NIH has made a significant effort to create these opportunities for engineers to work in areas like cancer. Nevertheless, it can be hard to break into new areas. A lot of us studying biomaterials don't have traditional cancer biology training, so we are going think about the world a little bit differently.

You have worked extensively to increase diversity in bioengineering and related fields. What have you been working on in this regard and what have you learned from those efforts?

We are trying to increase diversity at all levels of the training pipeline. For instance, I run a high school program every summer for students from backgrounds historically excluded from STEM fields. This program attempts to bring the students into the laboratory to see what they can bring to different complicated science projects

I ran an NSF-funded REU site at the University of Massachusetts, Amherst for several years and hope to restart that program at Tufts University next summer. This program aims to bring undergraduate students from diverse backgrounds into the laboratories across campus to introduce them to working at the interface between materials and life sciences. Our department is also working hard to diversify the profession at the graduate student level. Finally, as part of BME UNITE (Underrepresented Needs In Technology & Engineering), I have published several papers on strategies for diversifying the profession at the faculty level.

NIH Supplement Awards Help Support and Retain Women Faculty

With the support of an Administrative Supplement for Continuity of Biomedical and Behavioral Research Among First-Time Recipients of NIH Research Project Grant Awards (NOT-OD-23-032), Lewina O. Lee, Ph.D., Associate Professor of Psychiatry at the Chobanian and Avedisian School of Medicine at Boston University, and Clinician Investigator at the National Center for Posttraumatic Stress at the Veterans Affairs (VA) Boston Healthcare System, was able to accelerate her research's recovery from delays stemming from the COVID-19 pandemic and her infant daughter's surgery. She applied for and received this award in the final year of her RF1 award from the NIH National Institute on Aging. Her RF1 project was centered on launching the Boston Early Adversity and Mortality Study (BEAMS), which involved developing, implementing, and evaluating a new approach to large-scale administrative data linkage to enhance the value of long-running, observational human cohort studies of aging and to enable more rigorous research on the lifelong sequelae of early adversity. During that year, her infant daughter was diagnosed with a health condition and underwent a major surgery, and her research team was navigating challenges arising from the COVID-19 lockdown and delays with their data contractor. "The pandemic and its aftermath amplified many stressors for my partner and myself as first-time, dual-career parents, such as challenges in arranging childcare, being isolated from family support, and travel considerations before vaccines were available for children," says Dr. Lee.

Lewina O. Lee, Ph.D., Chobanian and Avedisian School of Medicine, Veterans Affairs Boston Healthcare System

Because of the supplement, Dr. Lee was able to contract with the Boston University Biostatistics and Epidemiology Data Analytics Center (BEDAC) to leverage its expertise to process a large volume of administrative data and thoroughly document the process. The funds also extended the tenure of key project staff and supported their travel to scientific meetings and a training session. "These funds have been critical for my career," says Dr. Lee, "because they allowed me to complete the planned activities and generate the high-quality publications crucial for subsequent grant applications." The funds also provided a source of encouragement during a stressful time. "It meant so much to me that my career and my work continued to matter, despite my disrupted productivity. This experience has encouraged me to keep charging forward to produce my best and most rigorous work," says Dr. Lee.

In 2019, Katie C. Coate, Ph.D., was awarded a Research Supplement to Promote Re-Entry, Re-integration into, and Re-training in Health-Related Research Careers (NOT-OD-23-170), which allowed her to resume pursuing a biomedical research career after serving as a full-time teaching faculty member at Samford University for several years. Trained as a basic scientist, Dr. Coate received a Ph.D. in molecular physiology and biophysics from Vanderbilt University and completed a postdoctoral fellowship in pharmacology at the University of Texas, Southwestern Medical Center. After completing her fellowship, she decided to accept a full-time teaching faculty position in the Department of Nutrition at Samford University, a decision based in part on her desire to start her own family while living close to relatives. Although she

Katie C. Coate, Ph.D., Vanderbilt University

immersed herself in teaching and mentorship and experienced great success as an educator and leader while at Samford, she realized that her true passion lay in scientific research.

Dr. Coate therefore applied and received a re-entry supplement, which provides support for mentored research training experiences for individuals with a high potential to re-enter an active research career. With this support, in 2019, Dr. Coate became a Research Instructor in the Division of Diabetes, Endocrinology, and Metabolism at Vanderbilt under the mentorship of Drs. Al Powers and Roland Stein. She has since been promoted to a tenure-track position as an Assistant Professor of Molecular Physiology & Biophysics at Vanderbilt, where her laboratory is studying pancreatic islet biology and diabetes.

"This re-entry supplement has had a tremendously positive impact on my professional development and career trajectory," says Dr. Coate. "It allowed me to resume my research activities under structured mentorship from established investigators and provided the time I needed to develop new scientific directions that facilitated my transition to independence."

IN THE JOURNALS

Two Studies Identify Rare Genetic Variants Associated with Early Menopause

(Original research by S. Stankovic et al., 2024. Nature. DOI: 10.1038/s41586-024-07931-x and A. Oddsson et al. 2024. Nature Genetics. DOI: 10.1038/s41588-024-01885-6)

Women vary considerably in rates of ovarian aging and the age at which they experience menopause. Both genetic and environmental factors affect the age at which women experience menopause. Two studies published in September 2024 in *Nature* and *Nature Genetics* have identified new, rare genetic variants with substantial impacts on age at menopause. Using data from the UK Biobank study on more than 100,000 women, Dr. Stankovic and colleagues identified genetic variants in five protein-coding genes associated with large differences in age at menopause. Most notably, protein-truncating variants in ZNF518A were associated with undergoing menopause an average six years earlier than other women (the average at menopause for U.S. women is 52).[1] Previous research has shown that common variants in ZNF518A are also associated with later age at puberty, suggesting that women carrying variants in this gene may experience considerably truncated reproductive lifespans.[2] Similarly, Dr. Oddsson and colleagues performed a genome-wide association analysis using a recessive model to search for rare, homozygous variants affecting age at menopause among more than 170,000 women from the United Kingdom, Iceland, Denmark, and Norway. This analysis revealed that women homozygous for a stop-gain variant in CCDC201 experience menopause nine years earlier than other women on average. Approximately 1 in 10,000 northern European women has this genotype, and roughly half experience primary ovarian insufficiency (ovaries that stop working properly before age 40). As a result, women with this genotype have fewer children and have their last child an average of five years earlier than other women.

Biomarkers in Cervico-Vaginal Fluid Show Promise for Detecting Endometrial Cancer

(Original research by K. Njoku et al., 2024. eBioMedicine. DOI: 10.1016/j.ebiom.2024.105064)

Endometrial cancer is the sixth leading cause of cancer deaths among women, and its incidence has been rising in the U.S. and several other developed countries. Leveraging proteomics, Dr. Njoku and colleagues analyzed cervico-vaginal fluid and blood samples from postmenopausal women with and without endometrial cancer. They then used machine learning to identify the proteins in these samples that best discriminated between women with and without cancer and to construct a five-biomarker panel of proteins found in cervico-vaginal fluid. This panel detected endometrial cancer with an area under the curve of 0.95. The cervico-vaginal panel outperformed a similarly derived panel based on proteins found in blood plasma, underscoring the potential utility of uterine-derived secretions for assessing gynecological health.

References

1. What is menopause? Published online October 16, 2024. Accessed November 6, 2024. https://www.nia.nih.gov/health/menopause/what-menopause.
2. The LifeLines Cohort Study, The InterAct Consortium, kConFab/AOCS Investigators, et al. Genomic analyses identify hundreds of variants associated with age at menarche and support a role for puberty timing in cancer risk. *Nat Genet*. 2017;49(6):834-841. doi:10.1038/ng.3841

The 61st Meeting of the NIH Advisory Committee on Research on Women's Health Spotlights Innovation in Women's Health Research

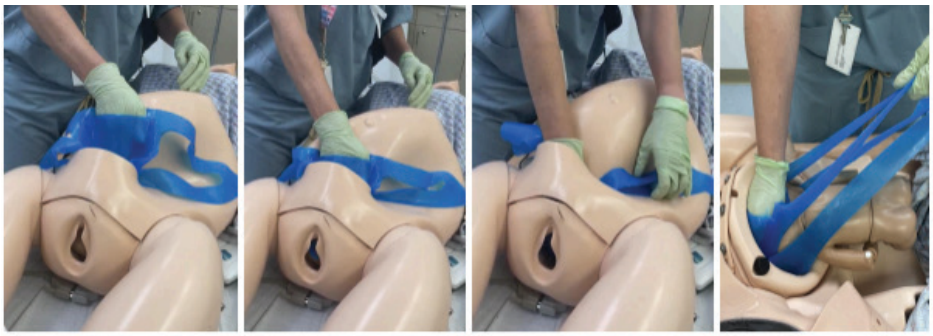
On October 8, 2024, the NIH Advisory Committee on Research on Women's Health (ACRWH) held its 61st meeting. ACRWH is a Federal Advisory Committee that was established in 1993 by the NIH Revitalization Act of 1993 to advise ORWH on NIH research activities concerning women's health, review the women's health research portfolio and goals for scientific career development, and assess the inclusion of women and minorities in NIH clinical research. ACRWH meetings provide a forum for ACRWH members' input regarding advancing women's health and sex differences research.

ACRWH Executive Secretary and ORWH Deputy Director Vivian Ota Wang, Ph.D., FACMG, CGC, called the meeting to order, and ACRWH Chair and ORWH Director, Janine A. Clayton, M.D., FARVO, delivered remarks on innovative approaches to accelerating research on women's health and sex differences. She highlighted ongoing NIH efforts to advance a lifespan approach to women's health research, including numerous programs focused on menopause, maternal mental health, the health of women belonging to historically underrepresented groups and living in rural areas, and other priority areas. She noted that these efforts are aligned with the *2024–2028 NIH-Wide Strategic Plan for Research on the Health of Women* that ORWH released earlier this year. She also highlighted that in partnership with multiple NIH Institutes and Centers (ICs), ORWH has created a National Women's Health Roundtable series promoting education and outreach for topics affecting women's health.

ORWH aims to accelerate research on health conditions that are female specific or that differentially or differently affect women. Notably, many of these conditions, such as heart disease and autoimmune disorders, span traditional research fields. In recognition of this fact, and in alignment with the White House Initiative on Women's Health Research, Dr. Clayton shared that NIH is directing $200 million in funding to interdisciplinary women's health research projects and partnerships across multiple NIH ICs.

Dr. Bruce J. Tromberg Highlights Innovations in Bioengineering, Computational Techniques, and Biomedical Imaging That Are Transforming Women's Health Research and Clinical Care

Following Dr. Clayton's ORWH Director's Report, Bruce J. Tromberg, Ph.D., Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), discussed how bioengineering, imaging, and computational techniques and the development of medical devices can transform the landscape of women's health research and clinical care. He noted that the Rapid Acceleration of Diagnostics Technology (RADx Tech) for Maternal Health challenge is promoting the development of at-home and point-of-care wearables, devices, and



Silicone sleeve designed by a DEBUT Challenge award undergraduate team to assist with cesarean delivery. (Source: Cesarean Delivery Glove video, courtesy of Alexis Chan, Gabriella Desch-Obi, Aidan Smires, and Priya Dave)

remote-sensing technologies to improve postpartum maternal health care. NIBIB also has partnered with ORWH to issue a challenge to accelerate the development of innovative technologies to improve the diagnosis of endometriosis—a condition that affects approximately 1 in 10 women and for which diagnostic delays are common. He spotlighted some remarkable work by students who have received Design by Biomedical Undergraduate Teams (DEBUT) Challenge awards, including a redesign of the speculum (a device unchanged in more than 200 years of use), the development of menstrual pads that can collect blood samples, and the creation of a silicone sleeve to help facilitate cesarean delivery (as shown in the image above). In addition, Dr. Tromberg highlighted the remarkable increase in women receiving undergraduate and graduate degrees in biomedical engineering and other engineering fields since 2005, as shown in the column chart below.

Bruce J. Tromberg, Ph.D., National Institute of Biomedical Imaging and Bioengineering

Dr. Susan S. Margulies Highlights Collaboration Opportunities in Science and Engineering Research Relevant to Women's Health

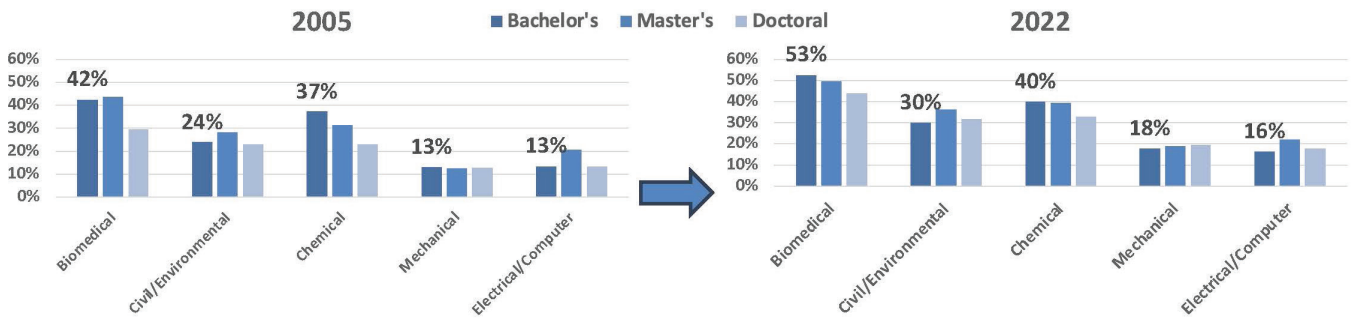
The Assistant Director for the National Science Foundation's (NSF) Directorate of Engineering, Susan S. Margulies, Ph.D., described NSF's approach to funding disease-agnostic areas and then transitioning research areas to agency partners for disease-specific funding. Dr. Margulies shared several ways in which NSF is accelerating high-risk, high-reward basic research on women's health to de-risk subsequent disease-specific and translational research. Notably, the Engineering Research Visioning Alliance, which identifies and catalyzes engineering research horizons and priorities with input from a diverse array of stakeholders, held a visioning event in June 2024 on Transforming Women's Health Outcomes Through Engineering. In addition, NSF recently funded two conferences on engineering solutions for women's health and using artificial intelligence (AI) to better understand menopause. NSF has published a Dear Colleague Letter that details its commitment to funding scientific and engineering research with an impact on women's mental and physical health.

Susan S. Margulies, Ph.D., National Science Foundation

Meeting attendees also heard from Matthew McMahon, Ph.D., Director of the NIH Small Business Education and Entrepreneurial Development Office on NIH SEED funding, from Eve J. Higginbotham, M.D., S.M., M.L. Vice Dean, Inclusion, Diversity and Equity; Senior Fellow, Leonard Davis Institute of Health Economics; Professor of Ophthalmology, Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, who presented on the NASEM Report on Advancing Research on Chronic Conditions in Women, and a panel focused on Technology,

Women in Engineering: *Students*

Percentage of Engineering Degrees Awarded to Women



Engineering, and Innovation in Women's Health Research.

The meeting agenda as well as a recording of the 2024 annual meeting are available online.

ORWH Hosts the Specialized Centers of Research Excellence on Sex Differences 2024 Annual Meeting

ORWH Senior Research Program Officer Rajeev Agarwal, Ph.D., and ORWH Director Janine A. Clayton, M.D., FARVO, provided opening remarks at the Specialized Centers of Research Excellence (SCORE) 2024 Annual Meeting on September 30, 2024. Victor J. Dzau, M.D., President of the National Academy of Medicine, delivered the keynote address on "The National Academies and Women's Health: Past, Present, and Opportunities for Progress," Dr. Dzau stressed the need for adequate funding for women's health research. He noted the importance of including pregnant and lactating women in clinical trials, understanding how social factors influence health outcomes among women, and increasing funding for women's health research. Following Dr. Dzau's remarks, Carolyn M. Mazure, Ph.D., Chair of the White House Initiative on Women's Health Research gave the capstone address. Dr. Mazure emphasized that the longstanding underrepresentation of women in research has led to a lack of data on how to prevent, diagnose, and treat numerous conditions that solely affect women, or that predominantly or differently affect them. She described how the White House Initiative is galvanizing interdisciplinary efforts across federal agencies, including the NIH, the Food and Drug Administration, and the Centers for Disease Control and Prevention, to advance women's health research and accelerate the translation of research findings into clinical care.

The SCORE on Sex Differences is a signature program of ORWH and the only NIH cooperative agreement program that supports disease-agnostic research on sex differences. Each SCORE center serves as a national resource for translational research on the role of biological sex differences in the health of women. SCORE leadership also works to develop and promote standards and policies for studying sex as a biological variable.

The Building Interdisciplinary Research Careers in Women's Health 2024 Annual Meeting Showcases Innovative Research by Early Career Investigators

On October 1, 2024, mentors, early career investigators, and scientific leaders heard presentations on innovative research conducted by Building Interdisciplinary Research Careers in Women's Health (BIRCWH) scholars on a diverse range of topics, including gene expression, military sexual trauma, and placental influences on infant health. Abbey Berenson, M.D., Ph.D., M.M.S., Director of the University of Texas Medical Branch Center for Interdisciplinary Research in Women's Health delivered the Ruth L. Kirschstein Memorial Keynote Lecture, in which she stressed the pivotal roles of mentorship and collaboration for driving innovation in women's health research. Nina F. Schor, M.D., Ph.D., Deputy Director for Intramural Research at NIH, delivered the Legacy of Leadership Lecture, which focused on cultivating the next generation of scientific leaders in biomedical research. A recording of the meeting is available online.

The BIRCWH program is an NIH-wide collaborative effort, co-sponsored by numerous NIH ICs and led by ORWH. ORWH works with the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute on Drug Abuse to provide grants management for the awards. Eligible postdoctoral fellows, instructional faculty, and junior faculty have recently completed clinical training or postdoctoral fellowship and plan to conduct interdisciplinary basic, translational, behavioral, clinical, and/or health services research relevant to women's health. Following participation in the BIRCWH program, most BIRCWH scholars obtain independent NIH grant funding.

UPCOMING EVENTS

Health Influences of Gender as a Social and Structural Variable Webinar
January 14, 2025, 11 a.m. – 1 p.m. EST

Small Business Opportunities for Innovative Women's Health Research (Virtual Only)
January 29, 2025, 11 a.m. – 1 p.m. EST

Diverse Voices: Reaching Rural Women: Implications for Research on Pregnancy
January 30, 2025, 3 – 4 p.m. EST

OADR-ORWH ScienceTALKS, Cell Therapies: A New Frontier for Autoimmune Diseases
March 4, 2025, 12 – 2 p.m. EST

Diverse Voices: Utilizing Vaginal Specimens to Identify Cancer
March 27, 2025, 3 – 4 p.m. EST

NIH Launches Discovery Portal for Women's Health Research

In partnership with the National Library of Medicine (NLM), ORWH launched the first phase of Discover Women's Health Research (DiscoverWHR), a discovery resource for NIH women's health research information. DiscoverWHR is a centralized resource for patients, their caregivers, medical professionals, researchers, and the public. The portal currently contains information concerning menopause, polycystic ovary syndrome, and selected autoimmune diseases (lupus, rheumatoid arthritis, and scleroderma). For each of these topics, Discover WHR contains information on funding opportunities, awarded projects, recruiting and upcoming clinical trials, recent research literature, and patient-friendly summaries. In subsequent phases, ORWH and NLM will add additional NIH-funded research topics and resources and incorporate data science tools. The *2024-2028 NIH-Wide Strategic Plan for Research on the Health of Women* and feedback from portal users will inform the selection of future research topics. The overarching goal of the portal is to facilitate research discovery by sharing information on NIH-supported grants, intramural research, clinical trials, and literature on issues that uniquely, disproportionately, and/or differently affect women across the life course.

Opportunity Map Highlights Areas of Research Relevant to Women's Health Ripe for Innovation

Relative to its impact, women's health has received relatively little investment in research and development. Fortunately, organizations across multiple sectors have started to address this funding gap. In July 2023, to align these organizations' efforts and facilitate cross-sector partnerships, ORWH and the Bill & Melinda Gates Foundation convened the Innovation Equity Forum—a global community of more than 250 key stakeholders from more than 50 countries. Based on stakeholder input, ORWH and the Bill & Melinda Gates Foundation created an opportunity map that highlights 50 high-return opportunities for innovation in global women's health. Some notable opportunities include (1) developing AI tools to incorporate qualitative information into the design and develop innovative products and interventions; (2) supporting technology transfer and training for these AI tools to ensure they are widely available and adopted across geographic regions; (3) augmenting efforts to include sex- and gender-related considerations when designing diagnostic, monitoring, and treatment tools for people living with dementia and their caregivers; and (4) developing improved, accessible contraceptive technology with fewer side effects and more prolonged efficacy.

ORWH Director Janine A. Clayton Inducted into the National Academy of Medicine

On October 21, 2024, in recognition of her outstanding professional achievements and commitment to service, ORWH Director Janine A. Clayton, M.D., FARVO, was elected as a member of the National Academy of Medicine (NAM). Election to NAM is one of the most prestigious honors in the fields of health and medicine.

Janine Austin Clayton, M.D., FARVO
Director, NIH Office of Research on Women's Health
NIH Associate Director for Research on Women's Health

Colorado College Awards ORWH Deputy Directory Vivian Ota Wang '83 Its Dr. Margaret A. Liu '77 Health Justice Award

In August 2024, Colorado College awarded ORWH Deputy Director Vivian Ota Wang, Ph.D., FACMG, CGC, its prestigious Margaret A Liu '77 Health Justice Award. This award recognizes alumni, students, staff, and faculty who demonstrate exceptional commitment to the goal of creating a more just and equitable world.

Acting President Manya Whitaker (left) and Vivian Ota Wang '83, recipient of the Dr. Margaret A. Liu '77 Health Justice Award

FUNDING OPPORTUNITIES

Advancing Health Equity through Interventions to Prevent and Address Housing Instability (R01 Clinical Trial Optional) (RFA-NR-25-001) Applications due by December 13, 2024

PHS 2024-2 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (PA-24-247) (PA-24-248) Applications due by January 5, 2025

PHS 2024-2 Omnibus Solicitation of the NIH and CDC for Small Business Innovation Research Grant Applications (PA-24-245) (PA-24-246) Applications due by January 5, 2025

Notice of Special Interest: Support for Conferences and Scientific Meetings to Support Consensus Building for Autoimmune Disease Research Related Common Data Elements (NOT-OD-24-145) Applications due by December 14, 2026

Interventions to expand cancer screening and preventive services to ADVANCE health in populations that experience health disparities (R01, Clinical Trial Required) (PAR-25-098) Applications due by January 8, 2027

Women's Health Research (NOT-OD-24-079) Applications due by November 5, 2027

STAFF UPDATES

Raven Hardy Richard, Ph.D.

In September, **Raven Hardy Richard**, Ph.D., joined the ORWH Interdisciplinary Research Section as a Health Science Policy Analyst. Dr. Hardy Richard received her Ph.D. in neuroscience from Emory University, where she was awarded a Health Policy Research Scholars Fellowship from the Robert Wood Johnson Foundation. Her graduate work focused on the neural correlates of cognitive and behavioral deficits in people living with sickle cell disease and in women from marginalized and traumatized populations. Prior to joining ORWH, Dr. Hardy Richard was a Genomic Science and Health Equity Fellow with the NIH National Human Genome Research Institute (NHGRI) and the Food and Drug Administration Office of Minority Health and Health Equity. At NHGRI, she focused on using bioinformatics to reduce health inequities in blood transfusion outcomes. Throughout her career, she has led a wide range of projects that leveraged interdisciplinary approaches to improve health equity.

Jielu Lin, Ph.D.

In October, **Jielu Lin**, Ph.D., joined ORWH as a Lead Data Science Core in the Immediate Office of the Director. Prior to this appointment, Dr. Lin served as a contractor statistician for ORWH. Dr. Lin received her Ph.D. in sociology from Case Western Reserve University. Following her graduate work, she served as an Assistant Professor at Northern Arizona University and then as a Staff Scientist at NHGRI.

For up-to-date information, visit www.nih.gov/women.

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