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A Message from our CEO



I'm delighted to bring you the Summer 2022 edition of *HMRI Insights*. Long-time HMRI supporters and staff may recognize the name: it was the title of our newsletter from 2007 to 2016. In reviving *Insights* and giving this HMRI tradition a new format, we aim to improve the way we share stories about our current research on the heart, the brain and the intersection between the two, as well as news of our science education programs.

In this issue, we're spotlighting the work of several distinguished HMRI scientists. Dr. Robert Kloner, chief science officer and chair and scientific director of cardiovascular research, recently presented the surprising results of research on the correlation between erectile dysfunction drugs and reduction in major adverse cardiovascular events, such as heart failure. Dr. Anju Vasudevan, new chair and scientific director of the Department of Neurosciences, has conducted trailblazing research on blood vessel formation and regeneration that may one day lead to cures for common mental disorders. Dr. Nicole Purcell, new scientific director of education programs, leads our efforts to train future scientists.

I'm also excited to be partnering with Dr. Susan Kane, the first woman to chair our board. Her experience as a biomedical scientist and educator make her the ideal advocate for all things HMRI as we develop a roadmap for the organization's next decade.

Finally, I want to thank the Altadena Guild of Huntington Memorial Hospital, whose popular Home & Garden Tour benefitting HMRI returned in May after a two-year hiatus. The Altadena Guild has partnered with us for seven decades, providing financial and volunteer support in countless ways.

All the activity you'll read about in these pages is possible because of the generosity of our donors. You have our deepest gratitude for joining us in the search for solutions to widespread cardiovascular and neurological conditions. Together, we'll find ways to improve the health of millions.

Julia E. Bradsher, PhD, MBA
President and Chief Executive Officer

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Insights

SUMMER 2022

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Anju Vasudevan's quest to cure neuropsychiatric disease

One in four people around the world will suffer from a neuropsychiatric illness at some point in their life. Conditions like anxiety, depression and schizophrenia can be managed with medication, but currently no cures exist. Many of these disorders are thought to originate in the embryonic brain as blood vessels form.

For the last 15 years, Anju Vasudevan, PhD—recently appointed as chair and scientific director of HMRI's Department of Neurosciences—has been studying angiogenesis, the process that forms new blood vessels. This happens with the help of endothelial cells, which line the inside of blood vessels. These cells are busy multitaskers, constantly migrating, growing and differentiating to distribute oxygen and nutrients throughout the body. They also regulate inflammation, control blood flow and prevent coagulation, all necessary elements for healthy brain development.

Vasudevan began her neuroscience research in Germany, then completed postdoctoral work at Massachusetts General Hospital and Harvard Medical School. She was a faculty member at Harvard for 13 years before joining HMRI as associate professor and scientific director of neurovascular research in June 2020.

"There's more connectivity and collaboration for multi-disciplinary research at HMRI, and the science here is very connected with society," Vasudevan says. "It's only after I got to HMRI that I started thinking about my research from a patient perspective, and this change has really inspired me."

That inspiration is paying dividends. For years, the prevailing wisdom was that endothelial cells were uniform, and that blood vessel formation occurred passively as a response to neural signals. However, Vasudevan's research upends that theory, suggesting that endothelial cells are much more diverse and active in blood vessel development and that they also mold brain cell development.

"One of our key discoveries was that disruptions in brain blood vasculature during early developmental stages can lead to a disruption in mental health," she explains. Specifically, if the gamma-aminobutyric acid (GABA) pathway in blood vessels is disrupted, it can harm brain development. "That was a completely new way to look at mental illness, because the field has always been very focused on neurons and brain cells."

Vasudevan and her team are now using human stem cells to make malfunctioning brain-like endothelial cells in the lab. "We can then evaluate what's going wrong and try to correct it," she says. "We believe endothelial cells provide guidance cues for brain cells and neurons to grow. By fostering neurovascular interactions, we can contribute to repair and regeneration. That's been our major goal."

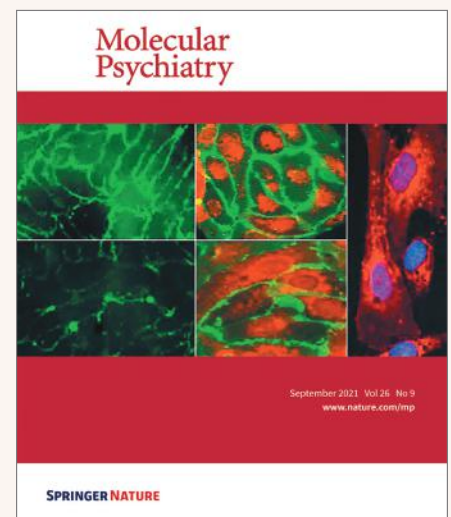
In 2020, Vasudevan and her colleagues demonstrated that a compound called nicotinamide adenine dinucleotide (NAD⁺) could stimulate changes in defective endothelial cells in mouse embryos, restore blood vessel formation and normalize brain development. If Vasudevan's ongoing research is successful, it could open the door to new therapies, perhaps even cures, for a host of neuropsychiatric disorders. That day may not be as far off as we think.



Anju Vasudevan with postdoctoral fellows

The cover of *Molecular Psychiatry's* September 2021 issue (below) featured images of endothelial cells from research conducted by Dr. Anju Vasudevan. The issue also contains a paper she co-authored, "Human forebrain endothelial cell therapy for psychiatric disorders."

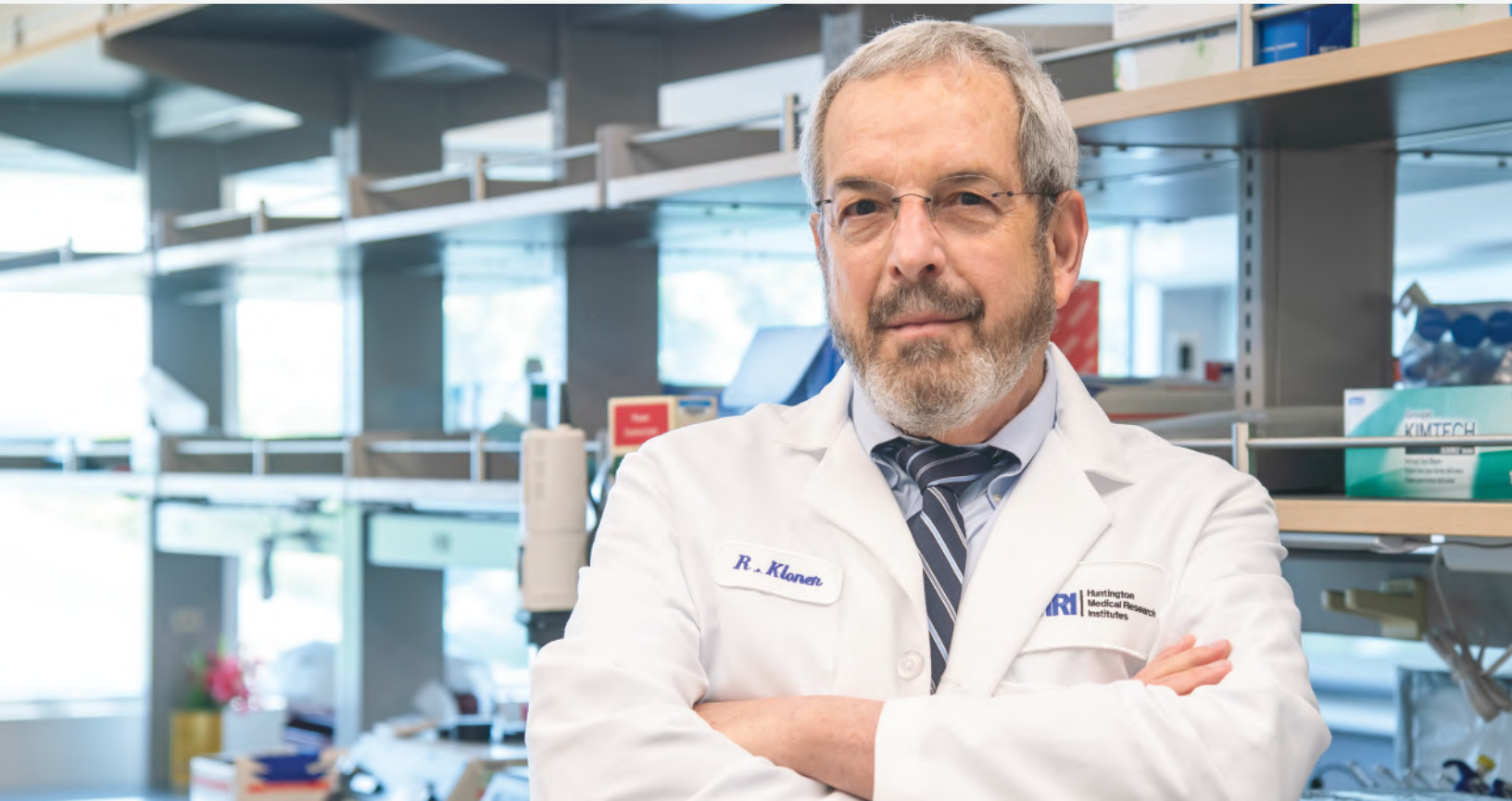
In March 2022, *Nature* magazine published Vasudevan's most recent article, co-authored with Dr. Robert Klöner and others, in its *Scientific Reports*. Titled "Gabbr3 endothelial cell-specific knockout mice display abnormal blood flow, hypertension, and behavioral dysfunction," the article highlights the presence of common molecular players in brain and heart vasculature that can lead to concurrent development of psychiatric and cardiac dysfunction.





Study uncovers hidden health benefits of erectile dysfunction drugs

The drugs may help prevent death and complications due to heart disease, according to large-population study led by HMRI's Robert Kloner



Robert A. Kloner

Every 36 seconds, one person in the United States dies from cardiovascular disease. That works out to a staggering 659,000 people each year—one in every four deaths. According to the Centers for Disease Control, heart disease is the leading cause of death in the nation.

A pioneering 14-year study funded by Sanofi and led by Robert A. Kloner, MD, PhD, chief science officer and scientific director of cardiovascular research at HMRI, suggests that common drugs used for erectile dysfunction (ED)—such as Viagra, Cialis and Levitra—are associated with significantly lower risk of major adverse cardiovascular event (MACE). Ironically, when these drugs first became available for ED,

men with heart issues were often advised not to take them as there were rare cases of heart attacks during sexual activity, even though there was no evidence that the drugs were the cause.

The first of these drugs, Viagra, was originally developed for treating angina pectoris, a type of chest pain that occurs due to narrowing of the coronary arteries. Viagra, Cialis and Levitra—known to scientists as “phosphodiesterase type 5 inhibitor” (PDE-5i) medications—are vasodilators, meaning they dilate blood vessels, which increases blood flow. That’s why they work so well for ED. In early trials, Viagra didn’t work very well at treating angina, but researchers discovered it had an effect on ED. Many of the risk factors for cardiovascular

disease are the same as the risk factors for ED, such as hypertension, diabetes, hypercholesterolemia, smoking and lack of exercise.

These commonalities intrigued Kloner and co-investigator Julia Bradsher, PhD, MBA, president and CEO of HMRI. Additional investigators included Eric Stanek, Christopher L. Crowe, Mukul Singhal and Rebecca S. Pepe of HealthCore Inc., and Raymond Rosen of University of California San Francisco. Using information collected from a large insurance database, the team examined statistical data on more than 70,000 men with ED, a uniquely large sample size suggesting high confidence in the results. The men were followed during a 14-year period for an average of two years, with the objective of comparing rates of MACE and death among men who had taken ED drugs to rates among men who had not.

“These drugs may have cardioprotective effects that could eventually go way beyond their current uses.”

“We initially looked at this study as a cardiovascular safety study, but we were surprised to see the association between the use of these drugs and the significant beneficial effects on cardiovascular outcomes,” says Kloner, who presented an abstract of the team’s findings at the American Health Association Quality of Care and Outcomes Research Scientific Sessions on May 13 in Reston, Virginia. The abstract was also published in *Circulation Quality and Outcomes*.^{*} “These drugs may have cardioprotective effects that could eventually go way beyond their current uses. Our findings provide hope that the association between taking ED drugs and reduced rate of adverse cardiac events will eventually lead to prospective clinical trials.”

The intriguing findings of the retrospective observational cohort study suggest that further clinical trials are indeed warranted. Among the men who took PDE-5i medications for ED compared to men who did not take these drugs, there was a 39% reduction in death due to heart disease; a 22% reduction in unstable angina; a 17% reduction in heart failure; a 15% reduction in the need for revascularization procedures like angioplasty, stenting and bypass surgery; a 13% reduction in MACE overall; and a 25% reduction in death due to any cause.

^{*} Kloner RA, Stanek E, Crowe C, Singhal M, Pepe RS, Bradsher J, Rosen R. The effect of phosphodiesterase-5 inhibitors on major adverse cardiovascular events and mortality in a large cohort of men with erectile dysfunction from a nationwide insurance database: a retrospective study [abstract]. *Circulation Quality and Outcomes*, 2022 May 12;15 Suppl_1:A195

Please check with your doctor before taking ED medications or any prescription drug.

Furthermore, men who had received more of a PDE-5i medication experienced greater reductions in MACE, including a 55% reduction in MACE in those with the highest amount of tablets dispensed versus those with the lowest amount.

While these results are encouraging, Kloner says that proving causality requires much more research. “Since this is a retrospective study, we can really only say that there’s an association between the use of PDE-5i drugs and major adverse cardiac events,” he explains. “To prove causality, a prospective, randomized clinical trial using placebos would need to be carried out. But there are signals that suggest that may be the case, especially given the fact that we saw a dose response. The higher the dose, the lesser the cardiac event rate.”

If PDE-5i drugs are proven to cause these effects, they could provide new therapies for preventing a number of adverse cardiovascular conditions. Kloner notes, “Another focus of our research is the study of new therapies to reduce the size of heart attack or reduce heart failure after a heart attack. Such therapies have the potential to save thousands of lives.”





Nicole Purcell aims to put HMRI education programs on the map

One of the first things you notice upon meeting Associate Professor Nicole H. Purcell, PhD, is her enthusiasm for teaching, a quality that makes her a natural fit for her role as scientific director of education programs at HMRI.



Nicole H. Purcell and postdoc fellow Khaja Shameem Mohammed Abdul, PhD

“I love working with students and knew I could make a difference here,” Purcell says. “I had great mentors throughout my career, and I believe all students should have the same opportunities I had, especially those who might not have access to hands-on science programs in their communities.”

Purcell grew up in a small coal mining region in Pennsylvania and attended nearby Susquehanna University. “I was exposed to biochemistry research there, and I knew that’s what I wanted to do,” she recalls. While earning her PhD by way of the University of Alabama and the University of Chicago, she came to focus on the cardiovascular system. “I liked understanding what was going on with the heart, and it really hit home with me,” she explains. “Both my grandfathers, whom I never knew, died from heart attacks.”

Purcell started a research laboratory at UC San Diego and taught in its Department of Pharmacology for almost 15 years. Looking to expand her research and mentorship opportunities, she made the move to HMRI in January 2021. “I wanted more collaboration where the research overlaps with mine. In addition to being a cardiovascular biologist I also study the heart-brain connection, so HMRI was a perfect fit,” she says.



As an HMRI associate professor, Purcell explores intracellular signaling pathways involved in cardiovascular disease.

Purcell hit the ground running when she joined HMRI. In addition to directing the 10-week Summer Undergraduate Research Fellowship (SURF) program, Purcell expanded the student volunteer program, opening it to high school students. “We pair them with a postdoc or an undergraduate and they work alongside them in the lab,” she explains. “It really gets them excited about science.”

Last year, Purcell and Education Program Director Carlos Aguirre, PhD, started HMRI’s Science, Technology, Engineering, and Mathematics (STEM) Program, a six-week program for high schoolers. The first cohort was small and virtual due to COVID, but this year they went live in June with 20 students—17 girls and three boys. The students are gaining research experience, including genotyping, dissection and other lab skills. At the end of the six weeks, students do a formal presentation and receive a stipend, which enables them to choose the STEM program instead of a summer job.

“I had great mentors throughout my career, and I believe all students should have the same opportunities I had.”

In addition to the SURF, STEM and volunteer programs, Purcell recently began directing postdoctoral programs at HMRI. Through these education programs, Purcell hopes to build upon three pillars. “One is access of opportunity for underrepresented students in underserved communities,” she says. “The second is community outreach to raise HMRI’s visibility as a leading biomedical research institute. And the third is mentorship. Whether they are high schoolers, undergrads or postdocs, we want to stay connected throughout their careers. We want to let them know HMRI will always help them. We want them to succeed.”



Board chair Susan Kane explains how donors drive scientific innovation

In January, HMRI's board of directors achieved a milestone: it elected the first woman chair in the organization's 70-year history. Susan Kane, PhD, will serve as chair for a two-year term. She brings a wealth of leadership, research and education experience to the role. She also brings contagious enthusiasm for HMRI's future and the impact of philanthropic support.

"It's an exciting time," she says. "Over the last three years we've been building our infrastructure. Now we're launching into a three-year strategic planning process that will focus on the sustained growth of our scientific research. Meanwhile, through our education programs, we're helping to diversify the pipeline of people going into science careers."

Kane's perspective on how a science organization can grow—and how education programs complement research—is shaped by her 25 years as a biomedical researcher at City of Hope, the renowned cancer-focused medical center in Duarte, California. Her many achievements there included serving as chair of the Department of Molecular Medicine at the medical center's Beckman Research Institute and as founding director of a postdoctoral training program in breast cancer research. She led an educational collaboration between City of Hope and Cal State LA as well as a K-12 STEM education program. She also helped direct an annual hands-on science experience for middle-school girls in Pasadena, where she is a long-time resident.

"All biomedical scientists strive to have an impact by expanding knowledge and improving health outcomes," she observes. "But a big part of our legacy is who we've trained and launched into the world as the next generation of scientists."

According to Kane, who has been a donor ever since she joined the board in 2015, philanthropic support is crucial to launching that next generation and to encouraging scientific innovation. She explains: "HMRI has a strong track record of receiving research grants. But contributions from private donors allow our scientists to do the pilot research that leads to private and government grants. Donor gifts enable young investigators, including our postdocs, to demonstrate to funders that they have viable research ideas. These young investigators drive innovation in science."

Altadena Guild brings back Home & Garden Tour to support HMRI

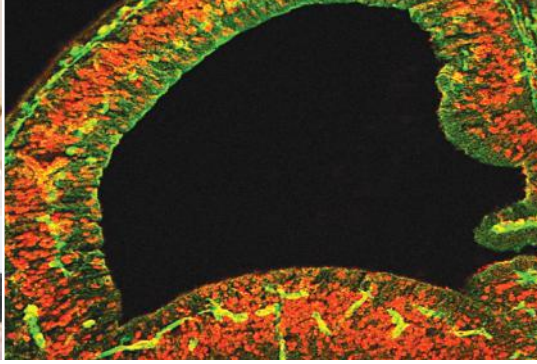


THE ALTADENA GUILD
OF HUNTINGTON MEMORIAL HOSPITAL

Since its founding in 1951, the Altadena Guild of Huntington Memorial Hospital has raised millions of dollars to benefit HMRI and Huntington Hospital. The Guild's trademark fundraising event is its annual Home & Garden Tour, which returned on May 1 after a two-year pandemic-imposed hiatus. This year's tour, the "Festival de Mendocino Lane," also featured live music, a craft sale, a café and cantina. It drew 1,200 people and grossed over \$130,000.

In addition to raising much-needed funds, the tour links the community and HMRI. Guild member and tour co-chair Elaine Bauer says that the event "contributes to making people aware of the important work being done by HMRI, the fellowships and student programs offered and the volunteer opportunities that exist within HMRI."

"Altadena Guild members understand the importance of continuing to support HMRI," Bauer notes. "HMRI researchers are internationally known for their contributions to science through programs focusing on heart disease, mental illness, migraine and Alzheimer's disease.... Advances in treatment will benefit us all." HMRI Chief Development Officer Jocelyn Ferguson says, "We are deeply grateful to the Guild for its loyal and generous support."



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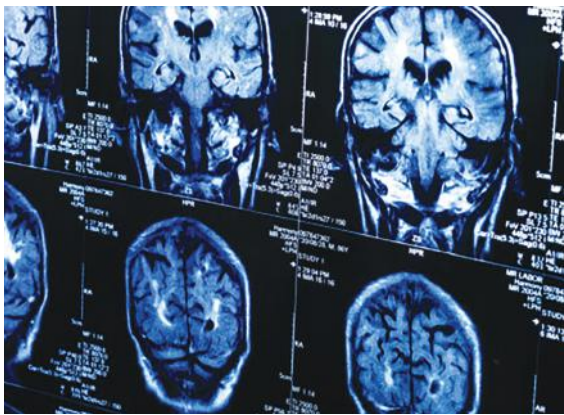
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You make scientific discoveries happen at HMRI

Tests that detect very early signs of Alzheimer's, enabling doctors to slow its progression. Therapies that reduce the size of heart attacks, increasing the odds of surviving them.

These are two of many promising discoveries taking place at HMRI right now—discoveries that can improve the health of millions. And it's all possible because donors like you give our researchers the funds they need to launch innovative research projects.



HMRI | Huntington Medical Research Institutes

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