

LANKENAU INSTITUTE FOR MEDICAL RESEARCH

CATALYST

FALL 2022-WINTER 2023

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About Lankenau Institute for Medical Research (LIMR)

LIMR is a nonprofit biomedical research institute located on the campus of Lankenau Medical Center and is part of Main Line Health. Founded in 1927, LIMR's mission is to improve human health and well-being. Faculty and staff are devoted to advancing innovative new approaches to formidable medical challenges, including cancer, cardiovascular disease, gastrointestinal disorders, autoimmune diseases and regenerative medicine, as well as population health. LIMR's principal investigators conduct basic, preclinical and translational research, using their findings to explore ways to improve disease detection, diagnosis, treatment and prevention. They are committed to extending the boundaries of human health through technology transfer and training of the next generation of scientists and physicians. For more information, visit limr.org.

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George C. Prendergast, PhD

*The Havens Chair for Biomedical Research
President and CEO
Lankenau Institute for Medical Research,
Main Line Health*

Connecting multiple types of research under one roof leads to broader understanding and investigation

Lankenau Institute for Medical Research (LIMR) is unlike most other research centers. Yes, we have innovative scientists who are experts in their fields. But what distinguishes LIMR is that these scientists are conducting basic and preclinical research, clinical research and population health research under one roof. This interconnection is yielding advances that we are proud to tell you about in this issue of *Catalyst*.

Our cover piece focuses on work from Charles Antzelevitch, PhD, and his colleagues. Their translational research on a natural molecule from safflower may help to prevent certain kinds of sudden cardiac death in young people. This research may also illuminate how older people develop atrial fibrillation. Studies of rare diseases often can deliver insights into more common ones as well.

We look at the work of Laura Mandik-Nayak, PhD, who is studying autoimmune disorders. To control autoimmunity, we currently use drugs that suppress the immune system as a whole. The search is on for a way to stop autoimmunity without affecting normal immunity. Building on the initial study of a gene I had discovered with Richard Metz, PhD, and Alexander Muller, PhD, Mandik-Nayak has spearheaded findings that IDO2 drives autoimmunity but has little if any effect on normal immunity. Her work has stimulated new drug approaches.

Mandik-Nayak focuses on rheumatoid arthritis, but she theorizes that her team's work will extend to other autoimmune diseases.

Various theories have attempted to explain the rise in autoimmune diseases and allergies in recent decades. Peanut allergies are an example of something that has gone from rare to commonplace. I believe three changes during the 20th century have contributed to this situation:

1. The environment in developed countries like ours is more sterile than ever before, thanks to improvements in sanitation, hygiene, antibiotics and vaccines. But our immune systems had evolved to cope with the “dirty,” germ-heavy environment that we lived in until recently. Humans have not evolved to this “cleaner” environment.
2. The explosive growth of global travel during the last several decades has led to a worldwide spread of microorganisms and substances that were once confined to specific regions of the world.
3. Man-made chemicals have increased exponentially, and we don't fully understand their long-term effects on our bodies. There are an estimated 20 million man-made chemicals, with the number continually growing.

Lastly, we look at the Lankenau Initiative to Improve Cardiovascular Access program. Lankenau Medical Center clinicians and the Main Line Health Center for Population Health at LIMR are collaborating to identify factors affecting care that are hidden from the physician, such as whether a person has transportation to a doctor's appointment or access to fresh fruits and vegetables. Our research is helping to identify barriers and improve comprehensive posthospital care. ★



A trailblazer in preventing sudden cardiac death

CHARLES ANTZELEVITCH, PHD, WAS A PIONEER IN UNDERSTANDING A MYSTERIOUS KILLER OF YOUNG MEN. HIS TEAM AND MAYO CLINIC MAY HAVE FOUND A NATURAL PRODUCT TO STOP IT.

Charles Antzelevitch, PhD, and his Lankenau Institute for Medical Research (LIMR) team have been partnering with the Mayo Clinic for the past four years on preventing a pair of rare deadly causes of sudden cardiac death. A breakthrough this summer shows that a traditional Chinese medicine from plants such as safflower may be an answer.

For Antzelevitch, the discovery is merely the latest of a series of advances he and his cardiovascular research team have achieved in exploring these hereditary conditions. The LIMR professor has been at the forefront of research to stop these killers for 35 years.

Antzelevitch's curiosity was first piqued by a U.S. government report on a mysterious syndrome responsible for a spate of deaths among young Southeast Asian refugees. The findings were not news in the refugees' native lands. In the Philippines, the mysterious syndrome was called *bangungot* (to rise and moan in sleep). In Japan, it was *pokkuri* (sudden unexpected death at night). In Thailand, it was *Lai-Tai* (died during sleep).

"It was also known as voodoo death," says Antzelevitch, executive director of LIMR's Cardiovascular Research Program. "Because it affected mainly young males primarily under 40, those in families that had experienced this would

go to sleep dressed in female clothes to ward off the evil omens thought responsible. As I learned more about these deaths, the stories intrigued me. My desire to save those with this devastating syndrome is what drove me then and continues to drive me today.”

Discovering and naming Brugada syndrome

Antzelevitch and colleague Gan-Xin Yan, MD, PhD, discovered an as-yet-unnamed condition while studying a type of arrhythmia (irregular heart rhythm) in experimental models. A chance encounter with a renowned French cardiologist on a bus during a conference in Florida led to a suggestion that Antzelevitch contact the Brugada brothers—Spanish arrhythmia specialists who had encountered cases with similar profiles in humans. “We started to work together, and it became clear that what the Brugas described in the clinic was what we saw in the laboratory,” Antzelevitch says. “They published their findings in 1992, and in 1996, Gan and I published our research, naming the syndrome after them.”

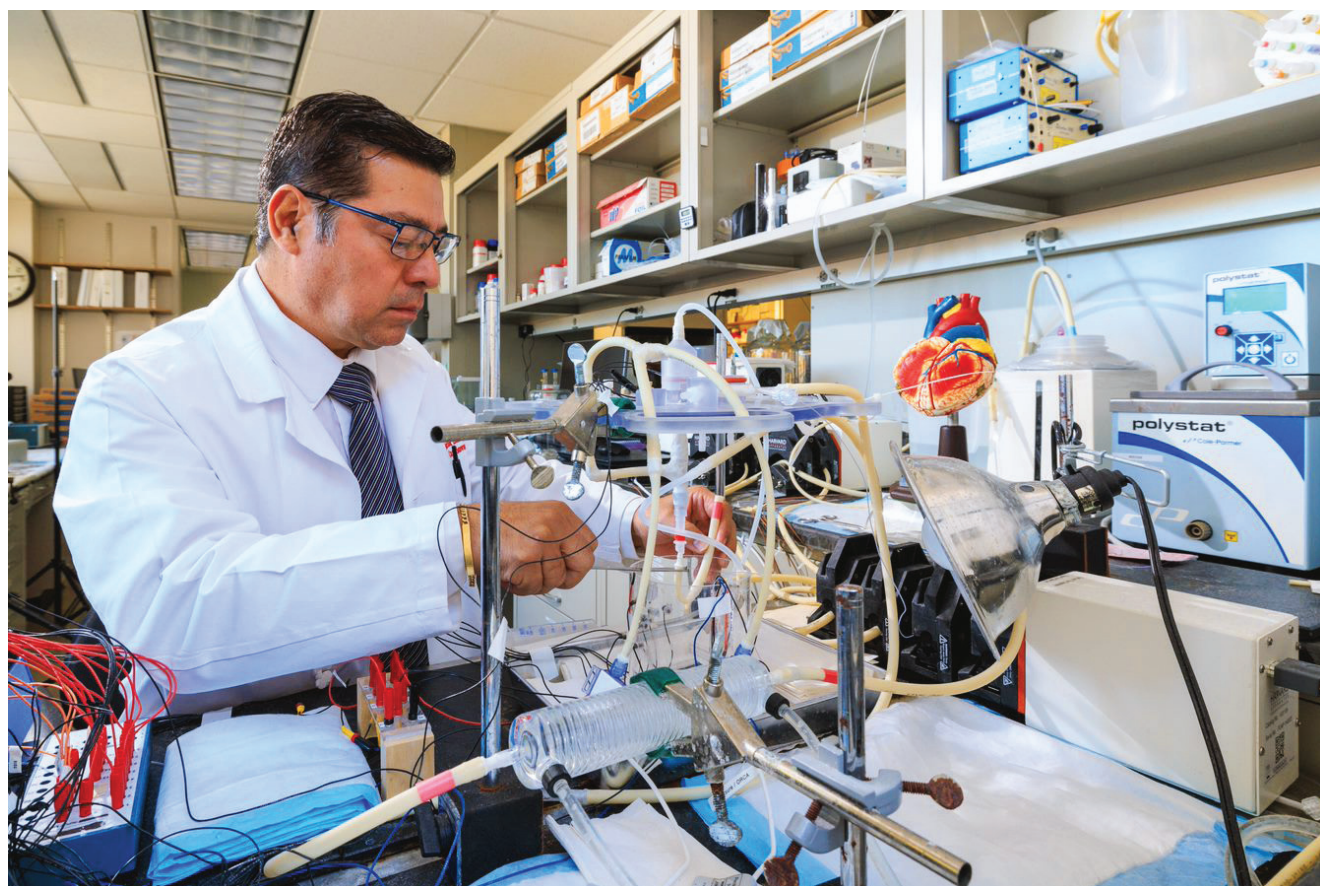
Unexplained fainting is one of the most common symptoms of Brugada. Once patients develop symptoms, there is a 50% chance they will die within 10 years. Some 150,000 Americans may be at risk of sudden death from Brugada.

Antzelevitch’s team soon discovered that Brugada had similarities to a second condition called early repolarization syndrome. Early repolarization is a common finding in electrocardiograms. However, recent studies show that this condition, previously thought to be benign, can sometimes lead to arrhythmias and sudden cardiac death. They then showed that the mechanisms involved were similar to those responsible for life-threatening arrhythmias that develop during hypothermia, or dangerously low body temperature.

Antzelevitch and his colleagues linked these cardiac conditions under a new name: J-wave syndromes.

The path to Mayo and a natural treatment

Based on their understanding of the mechanism underlying the J-wave syndromes, Antzelevitch and Yan in 1999



Héctor Barajas-Martínez, PhD, works with a three-dimensional heart model developed by colleague José Di Diego, MD, that mimics an inherited type of arrhythmia.

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COVER STORY

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suggested quinidine as the first pharmacologic treatment for the J-wave syndromes. Quinidine is one of the oldest drugs used to treat abnormal heart rhythms. What they had long sought, however, was a potassium channel blocker that selectively blocks a specific electrical current in the heart believed primarily responsible for these deadly syndromes. It eluded them for over 20 years.

During a conference several years ago, however, their luck changed. A doctor from Hong Kong, Gui-Rong Li, reported that a traditional Chinese medicine called acacetin blocks three electrical currents, including the one identified by LIMR as the culprit in the life-threatening arrhythmias. At Antzelevitch's request, Li sent some acacetin, and testing at LIMR found it to be extremely effective in preventing the dangerous arrhythmias.

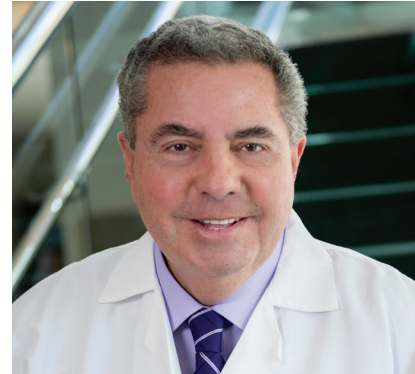
Acacetin has long been used in China for a range of conditions including rheumatoid arthritis, asthma, bronchitis, impotence and altitude sickness. It also has been reported to have strong anti-inflammatory and anticancer activity.

Eager to obtain clinical data on acacetin's effectiveness as an anti-arrhythmic, Antzelevitch contacted his friend Michael J. Ackerman, MD, PhD, at the Mayo Clinic and the collaboration with LIMR was launched. Ackerman's team at Mayo identified two patients with Brugada syndrome possessing mutations in the gene believed to be the culprit. LIMR research professor Héctor Barajas-Martínez, PhD, cloned the gene and showed in the lab that it increased the current they had determined was responsible for the sudden death syndromes and showed that acacetin blocked it, preventing the irregular rhythm. Also, José Di Diego, MD, developed a three-dimensional model of a heart with J-wave syndromes. The latest study was published in *Circulation: Genomic and Precision Medicine* in July 2022.

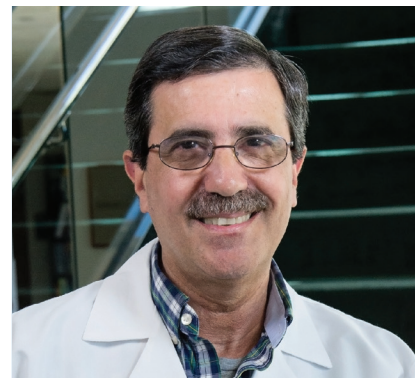
"We're fairly convinced this is going to be a safe drug," Antzelevitch says. "Its history of use in China for years gives us a lot of confidence."

LIMR's research with acacetin continues, but there are challenges. It has limited ability to dissolve in liquid, hampering efforts toward an FDA-approved drug.

So, LIMR is working to find a drug with similar features to acacetin but one that would be more soluble and at least as potent in blocking the current. "We need to find a drug that will selectively block the current that is at the heart of these sudden cardiac deaths," Barajas-Martínez says.



Charles Antzelevitch, PhD



José Di Diego, MD

"We still have a ways to go," Antzelevitch adds. "But I'm confident that we will ultimately arrive at an effective drug to protect patients afflicted with these syndromes. We are grateful to the individuals and federal funding agencies who made these studies possible, including Wistar and Martha Morris, who funded my early years at LIMR, as well as the W.W. Smith Charitable Trust." ★

The National Institutes of Health has provided \$2.93 million, or 95%, of the more than \$3 million in funding received to date.

Research on limiting surgical scarring receives national coverage



R. B. Claytor, MD, FACS

Research on the benefits of a technique to improve surgical scarring, led by R. Brannon Claytor, MD, FACS, was recently published in *U.S. News & World Report*.

Claytor, Chief of Plastic Surgery at Main Line Health and a Lankenau Institute for Medical Research clinical associate professor, demonstrated that a technique called microneedling helped surgical scars heal more attractively, especially if performed within a couple of months of surgery. Conventional wisdom had been to wait at least a year before attempting the procedure.

Microneedling is performed with a handheld device outfitted with 20 tiny needles that vibrate at over 100 times per second to create micro-punctures in the skin.

Claytor's publication, "Microneedling Outcomes in Early Postsurgical Scars" in the *Plastic and Reconstructive Surgery Journal*, demonstrated that early treatment of surgical scars was safe and that patients observed having better results with earlier intervention.

"Research and clinical evidence are key to pushing the envelope to achieve better results for our patients," he says. "In our next study, we plan to investigate the use of radio frequency with microneedling on scars." ✨

Heber-Katz honored as inaugural holder of endowed chair



Ellen Heber-Katz, PhD, was honored as inaugural chairholder of The Daniel B. and Florence E. Green Endowed Chair in Regenerative Medicine Research on Sept. 14. Pictured, from left, Phillip D. Robinson, then-President, Lankenau Medical Center; Peter H. Havens, Board Chairman, LIMR; Heber-Katz; Arlin S. Green, Green Family Foundation; George Prendergast, PhD, President and CEO, LIMR; and Alfred W. Putnam Jr., Chairman, Lankenau Medical Center Foundation.

Research showing how age affects metastatic melanoma growth in lungs featured in *Nature*

Marie Webster, PhD, was part of a team of researchers from Johns Hopkins, the Wistar Institute and the University of Pennsylvania whose findings on the role of aging in the outgrowth of metastatic melanoma in the lungs were published in the elite journal *Nature*.

Their research found that the lung microenvironment—the cells, molecules and blood vessels—in an older person promotes reactivation and faster growth of melanoma that has spread from its original site on the skin. In contrast, the lung microenvironment of a younger person restricts growth and may help keep the disease dormant. ✨

Mandik-Nayak's research brings autoimmune disease treatment closer

When Laura Mandik-Nayak, PhD, arrived at Lankenau Institute for Medical Research (LIMR) in 2006 as a young scientist devoted to exploring the causes of autoimmune disease, she found the institute's president and CEO immersed in efforts to find a way to turn on the immune system to fight cancer. The relevance to her area of study became immediately clear.

George Prendergast, PhD, president and CEO, and LIMR researcher Alexander Muller, PhD, felt stopping an enzyme believed responsible for shutting down the immune system held promise for cancer patients—but could leave those also suffering from autoimmune disease out in the cold.

"The immune system of someone with an autoimmune disease such as rheumatoid arthritis (RA) is already on overdrive, attacking the body's healthy cells as well as foreign bacteria and viruses," Mandik-Nayak says. "If you have autoimmune disease and you're waking up the immune system, you would expect that to make it worse."

But when they experimented on mice with RA, she says, "We found it was the reverse. It was turning off the arthritis."

The surprise marked the beginning of Mandik-Nayak's journey to find a drug targeting the enzyme indoleamine 2, 3-dioxygenase 2 (IDO2) to treat RA patients. That journey, she believes, will extend to numerous autoimmune diseases.

"I think the underlying causes of autoimmune diseases are probably pretty similar," Mandik-Nayak says.

"They may be using common pathways. With Type 1 diabetes, the immune system is attacking your pancreas. In the case of RA, it's attacking your joints and possibly other body systems, such as the skin, eyes, lungs and heart. With lupus, the attack is most widespread. The disease can potentially damage most of the body's tissues and organs."

Mandik-Nayak's reasoning about the similarities among autoimmune diseases is shared by the Myasthenia Gravis Foundation. She has received a pilot grant to determine if the lessons learned from RA apply to myasthenia gravis as well. In patients with myasthenia gravis, communication

between nerves and muscle is destroyed, resulting in weakness of the skeletal muscles and affecting the eyes, mouth, throat and limbs in particular.

Progress with RA remains the primary thrust. RA affects around 1% of the world population and can begin at any age, although the chance of onset is highest for those in their 60s. Women are two to three times more likely to develop the condition than men.

Of course, blocking the IDO2 pathway to treat RA is not as simple as turning off a switch. Mandik-Nayak and her team continue to search for an approach that's practical for treatment.

Initial studies with LIMR colleagues Lisa Laury-Kleintop, PhD, and Lauren Merlo, PhD, used a monoclonal antibody to target IDO2 that appears effective in preclinical RA models. However, the antibody's mechanism remains difficult to explain and efforts to obtain funding for further research have been challenging.

Mandik-Nayak's team also saw success with genetic material called small interfering RNA (siRNA), using a novel delivery system to protect and direct the siRNA used by retired LIMR professor Janet Sawicki, PhD, to inhibit the expression of proteins involved in cancer.

"However, even the protected siRNA has a short half-life," Mandik-Nayak says. "So you would need repeated injections. That means it might be difficult to translate into a feasible therapy. We need a better approach." ✨



Laura Mandik-Nayak, PhD, (second from right) leads a team of researchers in the fight against autoimmune disease. Others, from left: Weidan Peng, PhD; Lauren Merlo, PhD; and biomedical research assistant Neil Israni.



Mara Caroline, MD, and
Francis P. Sutter, DO, FACS

Helping low-income patients navigate barriers to care

NOVEL PROGRAM BRINGS COMPREHENSIVE CARDIAC TREATMENT AND RESOURCES TO THOSE IN NEED.

Cardiologists are accustomed to telling patients who have suffered a heart attack how to avoid another one. Giving up smoking, eating foods lower in cholesterol and exercising are just some of the directions they regularly provide aimed at restoring cardiovascular health.

But what if the patient can't get to cardiac rehab because they have no car? What if they can't afford fresh fruits and vegetables? What if family members are unsupportive?

"As an interventional cardiologist who cares for patients after a heart attack, I know that some will turn their lives around and some will have another event," says Mara Caroline, MD, head of the new Lankenau Initiative to Improve Cardiovascular Access (LIICA) program. "Then I start to look at why. It takes a multidisciplinary team to work through these issues."

LIICA is a collaboration between Lankenau Medical Center and the Main Line Health Center for Population Health Research (CPHR) at Lankenau Institute for Medical Research. It aims to identify and address barriers faced by low-income patients and deliver comprehensive posthospital care that might otherwise be inaccessible to them. It is believed to be the first program in the country to offer such wide-ranging services.

The pilot program is partially funded by philanthropy and was spearheaded by a donation from Steven A. Nichtberger, MD, who is a cardiologist and Main Line Health trustee, and his wife, Laura J. Bessen-Nichtberger, MD. Underserved patients

from surrounding low-income ZIP codes are identified as candidates when admitted to the hospital with a heart attack.

Caroline heads the program with the assistance of nurse practitioner Beata Kasia, DNP, CRNP. CPHR Executive Director Sharon Larson, PhD, worked with them to create a survey to identify these barriers.

"The program will evolve as we determine what the barriers are," Caroline says. "We've cast a wide net, but we're constantly surprised at what comes up—for example, transportation. If you have to take three buses and it takes three hours to get here, that's not doable."

LIICA also incorporates a broad range of health care professionals to address medical and psychosocial issues. Typical risk factors encountered include diabetes, smoking, high cholesterol, obesity and exercise deficiency. Pharmacists, community health educators and nutritionists have all stepped in to assist.

"Our colleagues are always eager to help," Kasia says. "They all want to do their part for these patients."

Every problem will be considered. Lankenau even provides patients in need with fresh produce from its on-campus Deaver Wellness Farm.

"We're trying to meet each person where they are," Caroline says. ✨



Meryl and Ben
Zuckerman

Decades of philanthropy to fight autoimmune disease

ZUCKERMAN FAMILY AUTOIMMUNE DISORDER RESEARCH FUND SUPPORTS LIMR RESEARCH TO PREVENT AND CONTROL AUTOIMMUNE DISEASE PROGRESSION.

They had been patients at Lankenau Medical Center many times, but it was not until the early 2000s that the late Ben and Meryl Zuckerman became acquainted with the groundbreaking autoimmune disease research at Lankenau Institute for Medical Research (LIMR). Their interest in supporting research efforts to find treatments for autoimmune disorders—specifically Type 1 diabetes and multiple sclerosis—stemmed from family members suffering from those diseases.

Over the next 15 years, Ben and Meryl personally contributed more than \$250,000 to support the work of LIMR scientists, including Laura Mandik-Nayak, PhD, Lisa Laury-Kleintop, PhD, and George Prendergast, PhD. Their generous philanthropy established the Zuckerman Family Autoimmune Disorder Research Fund with the Lankenau Medical Center Foundation. This research focuses on discovering therapeutic strategies to treat autoimmune diseases such as multiple sclerosis, lupus, rheumatoid arthritis and Type 1 diabetes. The Zuckermans were also instrumental in drumming up additional support, with friends and colleagues providing an additional \$225,000 to support this important work.

In recent years, the Zuckerman Family Autoimmune Disorder Research Fund has specifically supported Mandik-Nayak's efforts toward the development of new therapeutic strategies to prevent and control disease progression in autoimmune patients without hindering the immune system's ability to ward off disease and infection. Her focus is on rheumatoid arthritis, but she believes her work will extend to numerous other autoimmune diseases including Type 1 diabetes, lupus and myasthenia gravis.

"My parents always shared LIMR's goal of discovering ways to defeat autoimmune conditions that plague so many," says Ben and Meryl's son, Michael. "By providing personal financial support and asking others to contribute to the cause, my parents felt they were investing smartly to provide hope for those suffering from these debilitating autoimmune conditions now and far into the future."

Michael shares his parents' generous spirit and devotion to philanthropy—he has personally continued making contributions to autoimmune disease research as well as pulmonary medicine at Lankenau. "I am committed to continuing this philanthropy in their names for as long as I am able," he says. ★

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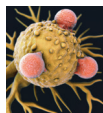
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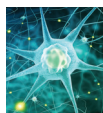
Your investments in research at LIMR can have a significant impact

You can designate one of the following funds to direct your contributions and support research that is important to you.



Immunotherapy Pioneer Fund

Immunotherapy entails the prevention or treatment of disease with substances that manage the immune system's capabilities to clear disease, rather than attack the disease itself. LIMR has spearheaded unique studies of disease modifier pathways that impact immunity and cancer progression, developing new drugs to target them. Your generous contributions to this fund will help us to continue to advance these innovative directions.



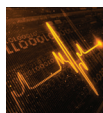
Regenerative Medicine Vision Fund

Regenerative medicine deals with new processes of replacing, engineering or regenerating human tissues to restore or establish normal function. LIMR is privileged to have one of the pioneers in regenerative medicine, Professor Ellen Heber-Katz, PhD, who has discovered an experimental drug approach that may eliminate a need for stem cell transfer. Your contributions to the Regenerative Medicine Vision Fund will help further her research.



Biotechnology Innovation Fund

This fund supports work on biological molecules engineered by LIMR scientists that can enhance the diagnosis, prognosis and treatment of disease. Your generous contributions to this fund can help advance the work of our researchers including, for example, our studies on targeted nano-carrier therapeutics as experimental treatments for cancer, and our work on cloned human antibodies as treatments for infectious disease, cancer and neurological illnesses.



Cardiovascular Breakthrough Fund

Cardiovascular disease accounts for nearly 800,000 deaths in the United States every year, or about one of every three deaths. Additionally, about 92 million American adults are living with some form of heart disease or the aftereffects of stroke. LIMR is home to world-renowned cardiovascular researchers. Your gift to this fund will further research that could benefit the lives of millions of heart disease and stroke patients.

Support Research Highlighted in This Issue

- **Lankenau Initiative for Improved Cardiovascular Access Fund** to investigate and address social determinants of health for underserved patients with cardiovascular disease
- **Zuckerman Family Autoimmune Disorder Research Fund** to support the discovery of therapeutic strategies to treat autoimmune diseases

LIMR Unrestricted Fund

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ABOUT MAIN LINE HEALTH

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