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## LIMR's research gets to the heart of how a robotic surgery can be game-changing

**A**t the Lankenau Institute for Medical Research (LIMR), we are committed to work that can significantly impact patients' lives, not simply answer questions that, although important, might accomplish little more than satisfy scientific curiosity.

In this issue of *Catalyst*, this commitment is illustrated in the cover story on how LIMR researchers worked with pioneering Lankenau Medical Center cardiac surgeon Francis Sutter, DO, to establish the merit of his robotic cardiac bypass procedure. Dr. Sutter has performed more than 2,500 robotic-assisted coronary bypass surgeries since 2005. Because his minimally invasive procedure involves only small incisions between the ribs, patients with coronary disease have been able to recover more quickly and easily than if they underwent conventional surgery, where the breastbone is broken and a heart-lung machine is used. Most importantly, elderly patients and those with comorbid illnesses who might have been unable to tolerate the conventional procedure are able to undergo bypass.

However, despite his work, only a handful of hospitals and doctors in the U.S. offer the robotic procedure, partly because they contend—even after nearly two decades—there is insufficient evidence of its safety and effectiveness to justify the expense and training.

Now, thanks to the work of LIMR researchers, those doubts can be put to rest. Aleksander Dokollari, MD, PhD, along with his colleagues in LIMR's Center for Cardiac Surgery Research, worked with Dr. Sutter to compare his surgical results over 16 years to those of top international clinical trials of nonrobotic heart bypass surgeries. They found that Dr. Sutter's rates of survival and complications were as good or better than the outcomes obtained in those trials. Dr. Dokollari presented

the results in January at one of the leading cardiac surgery conferences in the United States. I am thrilled we are getting the word out, and we will continue working to do so in hopes that, one day, robotic bypass will be offered at all medical centers across the country.

Another story in this issue focuses on Duet Therapeutics, a LIMR spin-off company, and its work to fight a diabetes complication called retinopathy—a leading cause of blindness in adults. Building on research led by LIMR principal investigators Alexander Muller, PhD, and Lisa Laury-Kleintop, PhD, Duet is seeking to develop an oral tablet to treat diabetic retinopathy before patients become symptomatic. By analogy, this tablet could provide a drug similar in impact to statins, which help prevent heart attacks.

Duet is just one of the latest success stories of our *acapreneurial™* approach, which blends academics with the advantages of entrepreneurialism. We believe Duet will succeed in developing this treatment and that it will have a tremendous impact on patients' everyday lives.

Lastly, we feature the work of veteran scientist James Mullin, PhD, whose work on the benefits of readily available micronutrients for gut health has turned toward fighting COVID-19 pneumonia. He has developed evidence that vitamin D strengthens the lining around the lung sacs, preventing fluid from leaking into the airways. I agree with Dr. Mullin's statement that because the potential benefits of taking a vitamin D supplement are so high, and the risks are little or none, physicians everywhere should be urging patients to take it.

I hope you enjoy our issue of *Catalyst*. ✨



## For coronary bypass patients, Lankenau shows a better way

### ROBOTIC-ASSISTED CORONARY BYPASS PROCEDURE DELIVERS RESULTS COMPARABLE TO CONVENTIONAL OPEN-HEART SURGERY—WITH AN EASIER RECOVERY.

**F**rancis Sutter, DO, chief of cardiac surgery at Lankenau Medical Center, pioneered robotic-assisted coronary bypass surgery in 2005 and has performed the minimally invasive procedure more than 2,500 times.

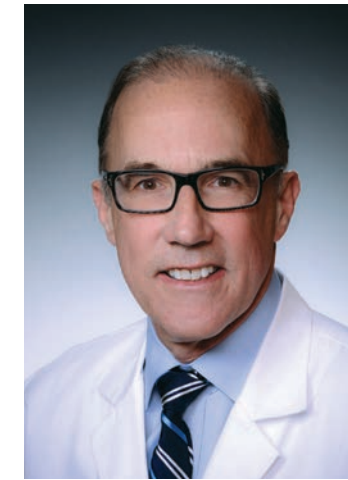
It is a remarkable number—and one that tells only part of the story. Many older patients who never could have tolerated traditional open-heart surgery instead were able to undergo heart surgery through a robotic procedure, recover and go on with their lives. Patients generally recovered much faster after robotic surgery compared to conventional surgery because it involved navigating through tiny incisions

between the ribs, not having the chest opened up, not having to stop the heart, and not having the breastbone cracked to access the heart's coronary arteries.

Doctors and hospitals have been hesitant to pursue robotic cardiac surgery even as years passed and the number of successful procedures mounted, often expressing that the long-term results were still to be proven. Now, thanks to scientists at the Lankenau Institute for Medical Research (LIMR), the evidence is clear that other hospitals in the region—and throughout the country—should follow Lankenau Medical Center's example.

They compared Lankenau Medical Center's results with those in groundbreaking international trials of nonrobotic heart bypass surgeries and determined that survival and complication rates were not only consistent with those outcomes but, in some instances, even better.

Says Dr. Sutter: "It's gratifying to see these accumulated results. I began performing the robotic procedure 18 years ago because the traditional open-heart method was often too traumatic for older patients. Even if you conducted the open procedure flawlessly, they tended not to fare as well. We now know for certain that robotic bypass surgery not only gives patients a better outcome but allows them to recover more quickly. I'm on a mission to teach what I've learned to other doctors. I want as many patients as possible to benefit from robotic bypass."



Francis Sutter, DO

### An option for many patients considered inoperable

Coronary artery bypass surgery is performed approximately 150,000 times a year in the United States alone. The numbers ought to be higher, says lead research investigator Aleksander Dokollari, MD, PhD. Many patients previously deemed inoperable because of their age or conditions such as diabetes and kidney disease that made them high-risk can benefit from the robotic procedure.

Dr. Dokollari and Dr. Sutter presented Lankenau's experience at one of the top conferences in the world for cardiac surgeons—the Society of Thoracic Surgeons (STS) 59th Annual Meeting in January.

"It's understandable why many hospitals and surgeons have been hesitant to adopt robotic bypass surgery," Dr. Dokollari says. "In the early days, the technology was less developed. The skill set was demanding and difficult to learn. Many weren't willing to push through the early obstacles. But now we have the blueprint for success. I believe others will begin to follow it."

### Best suited to operate on the 'widowmaker'

For the most part, robotic bypass procedures are best suited to reach the left anterior descending artery—also known as the "widowmaker," Dr. Sutter says. In 2021, 54.9% of all coronary artery bypass procedures performed



Monitors display high-definition, magnified images for the surgical team during the procedure.

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## COVER STORY

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at Lankenau were done robotically, according to the most recent annual STS reporting data, compared to 1.2% performed nationally.

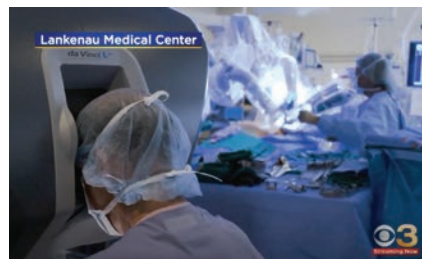
Some of the key results of LIMR's research have been as follows:

- The survival rate after 15 years for Lankenau bypass patients was comparable to that found in prior clinical trials even though the ages of the patients involved were older. On average, the Lankenau patients were 71 years old compared to 65 for those in the comparison trial.
- The low percentage of surgeries free of major adverse events (death, myocardial infarction, need for repeated procedure) was comparable to trial results published in the *New England Journal of Medicine* despite the same average age difference.
- Hospital complications such as postoperative atrial fibrillation and the need for transfusion due to bleeding were lower when compared to results of two trials.
- Length of stay was shorter (four days vs. eight for traditional bypass).

### No opening up the full chest, no stopping the heart

Medically, the main advantages of robotic surgery compared to traditional are simple to explain. "Opening the full chest means cutting the breastbone and spreading it," Dr. Dokollari says. "That leads to difficulty healing, more complications, more infections and longer lengths of stay. Critically important is that you don't have to stop the patient's heart and place them on a heart-lung machine."

The other coauthors of the study were Michel Pompeu Sá, MD, MSc, PhD; John Malin, DO; Serge Sicouri, MD; Gianluca Torregrossa, MD; MaryAnn C. Wertan, RN; and Basel Ramlawi, MD, chief of cardiothoracic surgery, Main Line Health.



### WATCH CBS PHILADELPHIA'S REPORT:

To learn more about this story, scan the QR code.

Dr. Dokollari has another potential cardiac advance in the works called the Lankenau Risk Score. Using information from a patient's profile—such as previous cardiac issues, family history and kidney disease—he believes doctors will be able to predict the person's five-year survival rate and risk of complications after bypass surgery (robotic or traditional). His proposal has reached the final round in the 2023 Innovative Project Award competition held by the American Heart Association. The winner is eligible for a \$200,000 award to pursue their project.

"Today, if you ask a surgeon how you will fare after bypass surgery, all they can do is give an educated guess," Dr. Dokollari says. "I believe this algorithm will remove the guesswork." ✨

## NEWS

### Antibodies created at LIMR playing key role in fight against polio



Scott Dessain, MD, PhD

Human antibodies cloned in the lab of Scott Dessain, MD, PhD, at the Lankenau Institute for Medical Research (LIMR) have been adopted by the World Health Organization (WHO) as a crucial part of its plan to permanently eradicate polio.

The WHO Expert Committee on Biological Standardization approved the antibodies as the standard for quality-control testing of all inactivated polio vaccines (IPVs) worldwide in late 2022 at a meeting in Geneva, Switzerland. The new test will increase assurance of the vaccines working properly when administered. The committee first advanced guidelines incorporating the LIMR antibodies to test IPV potency two years earlier.

The disease is believed to be quietly spreading throughout the world. Health officials in Philadelphia and other large metropolitan areas last year announced they will test sewage for poliovirus because of a case detected outside New York City and the subsequent detection of poliovirus in the New York region's sewage. ✨

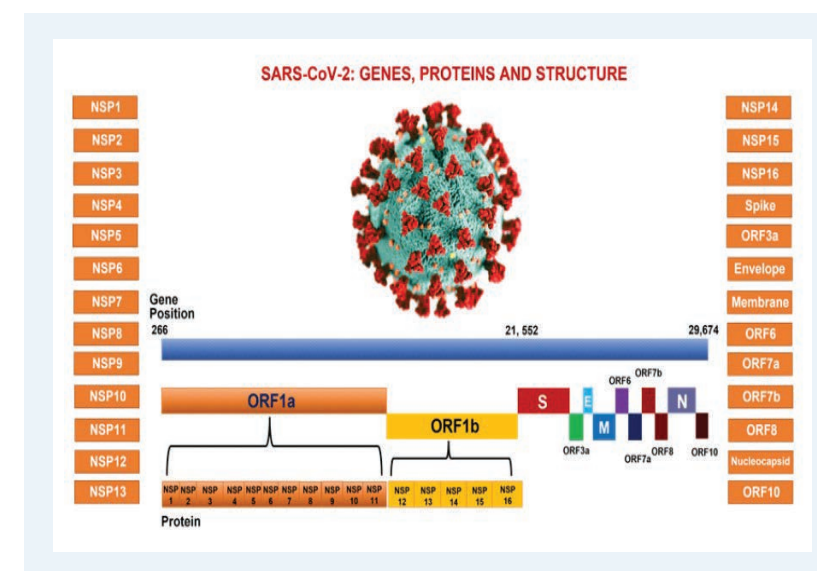
### Thomas creates world's first complete resource on structure of COVID-19 virus

Sunil Thomas, PhD, a Lankenau Institute for Medical Research (LIMR) vaccine expert, has created a groundbreaking resource for scientists seeking to develop new and more effective vaccines in the ongoing battle against COVID-19.

The COVID-19 Genetic Resource Guide—the world's first compendium of the genetic code and protein structure of SARS-CoV-2, the virus that causes COVID-19—went live on LIMR's website in February.

The first COVID-19 vaccines targeted the viral spike protein, the part of the virus that binds to human cells. However, the limitations and liabilities of these early vaccines are now evident, including that the spike protein can readily mutate and that the mutated virus can evade vaccines that target it.

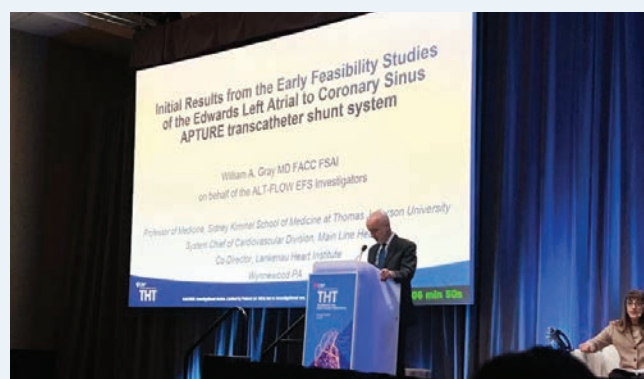
Dr. Thomas' COVID-19 Genetic Resource Guide provides molecular information on the spike protein as well as 25 other proteins of SARS-CoV-2. All are potential targets for vaccine development—individually and in combination. ✨



### Ablation safe, effective in treating atrial fibrillation

Research guided by Peter Kowey, MD, a Lankenau Institute for Medical Research professor and one of the nation's preeminent experts in treating arrhythmia, has delivered the most powerful evidence to date that catheter ablation is safe and effective in treating atrial fibrillation (AFib).

Dr. Kowey is senior author of a recent study in the *Journal of the American College of Cardiology* showing the procedure is successful in most patients, with few side effects. Researchers from the Mayo Clinic, Cleveland Clinic, Yale University, Johns Hopkins University and other top institutions conducted the study. As senior collaborator, Dr. Kowey was responsible for much of the process that produced the paper. ✨



Principal investigator William Gray, MD, had a simultaneous first-ever report of the data and journal publication in March on the outcomes of an international early feasibility study of a device treating symptomatic heart failure. The device, which offloads pressure from the left atrium to the right, was successfully implanted in 90% of patients, and demonstrated significant improvements in the patients' heart failure symptoms and elevated heart pressures. Dr. Gray presented at the Technology and Heart Failure Therapeutics 2023 conference in Boston. He is system chief of the cardiovascular division at Main Line Health, co-director of the Lankenau Heart Institute and a LIMR and Thomas Jefferson University professor.

## LIMR-backed start-up pursues drug to prevent diabetes-related blindness

**B**ecause of the high stakes, millions of patients with no noticeable symptoms take oral medication to lower cholesterol or blood pressure when their doctor detects early signs of heart disease. However, when it comes to diabetic retinopathy, a leading cause of blindness in adults ages 18–64, there is no comparable medication.

That's where Duet Therapeutics, a biopharmaceutical company spun off from the Lankenau Institute for Medical Research (LIMR), is aiming to step in. The company is working to develop and commercialize a potential drug for treating the earliest stages of diabetic retinopathy as well as another condition called wet age-related macular degeneration (AMD).

The goal is a new medicine that can be prescribed to patients diagnosed with early stages of the diseases during their regular eye exams, many years before their disease could become symptomatic if left untreated.

"If we can successfully develop a daily tablet to prevent patients from progressing to symptomatic retinopathies and vision loss, we will dramatically improve the quality of life of potentially millions of patients around the world and prevent many of them from progressing to loss of vision," says Sam Barone, MD, the company's president and chief medical officer. "That is our mission."

The hallmarks of advanced diabetic retinopathy and AMD are uncontrolled growth of new blood vessels in the delicate tissue at the back of the eye (retina) responsible for converting light into the electrical signals interpreted by the brain. Vision loss results when the aberrant growth leads to the leakage of fluids into the retina. Once these retinal

diseases, or retinopathies, have advanced, symptoms include blurred vision, black "floaters" and empty areas of vision.

The first effective treatment for diabetic retinopathy arrived in the early 2000s. It involved a then-new class of drugs that block vascular endothelial growth factor (VEGF), a protein that stimulates growth of new blood vessels. Anti-VEGF medication is effective but involves injections into the eyeball and is only used with advanced stages of disease, Barone says.

Scientific breakthroughs led by LIMR principal investigators Alexander Muller, PhD, and Lisa Laury-Kleintop, PhD, serve as the foundation of Duet's work. LIMR scientists discovered a previously unrecognized biology of an enzyme called indoleamine 2,3-dioxygenase-1 (IDO1), which was first identified in the 1990s as a regulator of the human immune response.

The LIMR team discovered IDO1 also plays a key role in the diseased retina through the production of a signaling molecule called interleukin 6, or IL6. The team proposed that IDO1 inhibitors could form a new class of medicine that could slow or prevent the progression of retinopathies. To support investment and commercialization, LIMR filed for, and has been issued, broad patent protection.

As a LIMR spin-off company, Duet is being supported in part by an investment from the Lankenau Medical Center Foundation's Breakthrough Medicines Fund.

Duet is now working to demonstrate in preclinical experiments that IDO1 inhibitors can reduce the fluid leakage that leads to vision loss and to confirm the drug gets into the retina itself. ✨

### LIMR Breakthrough Medicines Fund

The LIMR Breakthrough Medicines Fund presents a new way to support applied medical research. Charitable contributions to the fund will accelerate LIMR's ability to advance its most promising "bench to bedside" research by making seed investments in selected start-up companies connected to the Institute. Funding supports advanced research, helping companies address hurdles they face in unlocking mainstream institutional investment.

Any returns on the fund's investment will be deposited back into the fund in an evergreen sustainability paradigm to grow the fund and support future investments in LIMR start-up companies driving medical innovation.

This year, Duet Therapeutics has been selected as the LIMR spin-off company to benefit from philanthropic investments in the fund. The start-up is working to develop and commercialize a potential drug for treating the earliest stages of

diabetic retinopathy and wet age-related macular degeneration.

"Developing an entirely new class of medicines is a journey of many years and requires substantial investment of risk capital," says Simon Tomlinson, PhD, Duet's CEO. "The Breakthrough Medicines Fund will help LIMR spin-off companies start that journey."

**Please join us by making a gift today.**

## Vitamin D may be a lifesaver against COVID pneumonia, LIMR's Mullin finds

**V**itamin D benefits the body in many ways—from helping to keep bones strong to fighting infection and reducing inflammation. In recent years, early-stage research by Lankenau Institute for Medical Research (LIMR) scientist James Mullin, PhD, has pointed to another benefit: warding off pneumonia. Vitamin D appears to strengthen the lining around the lung sacs, preventing fluid from leaking into the airways.

Then the pandemic struck, and Dr. Mullin's area of research suddenly gained relevance that no one could have predicted. Waiting years for definitive research findings when there is little to no downside to taking a vitamin D supplement made no sense to him amid the COVID-19 emergency. He gave it to his own family right away and is striving to get the word out about the vitamin's potential in the fight against COVID pneumonia—a potentially deadly outcome of the virus.

"For COVID, the simplest, easiest thing I would have done both nationally and internationally would have been to put everybody on a vitamin D supplement," Dr. Mullin says. "I feel strongly that it can lessen the suffering associated with COVID illness. It's not going to prevent it or reduce your chances of getting it. But if you do get it, it should reduce the severity of illness. It may be the difference between merely 'feeling sick' vs. being in an intensive care unit or worse."

To Dr. Mullin and his research laboratory colleagues, many of the organs of the body have something in common. Most of them separate two compartments—the bloodstream on one side and a specialized space or fluid on the other side—

like urine in the kidney tubules or air in the lung sacs. Their ability to function is compromised if there are leaks in the junctional seals that surround the epithelial cells that form the linings of the major organs.



James Mullin, PhD

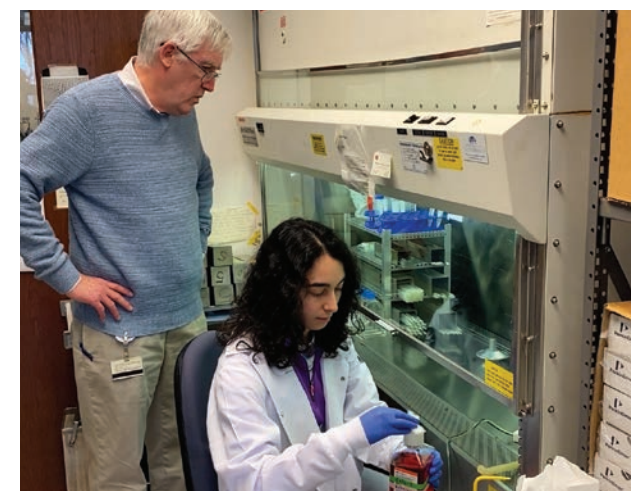
"It's just like a tile floor, where the tiles are the epithelial cells and the grout is the junctional seals," he says. "The junctional seals become leaky in just about every disease. They become leaky in cancer and chronic inflammation. They become leaky in a host of different infectious diseases, with COVID as one example. With COVID, fluid can leak and accumulate in the lungs, which puts a patient in the intensive care unit or, in extreme cases, on a ventilator."

His team is discovering that vitamin D is one of many micronutrients that can play a role in reducing leaks. Zinc appears highly protective in the gastrointestinal tract and the kidneys. Vitamin A, like vitamin D, appears to have an effect in shielding the airways. Findings were highlighted in an article published last year in the *International Journal of Molecular Sciences*, with LIMR colleagues Katherine DiGuilio and Elizabeth Rybakovsky among the coauthors. That vitamin D is inexpensive, safe and readily available should elevate it as an immediate area of focus, he says.

"One of the strongest predictors of a bad outcome for someone who contracted COVID was if they were vitamin D-deficient going into the illness," Dr. Mullin says. "If that's the case, that would put vitamin D deficiency right up there with obesity and diabetes, except that this deficiency is so easy to correct or alleviate."

Meeting the Food and Drug Administration's recommended daily allowance (RDA) for vitamin D and other micronutrients appears too low to provide this protective effect, Dr. Mullin says. The right amount is above the RDA levels but well below levels so high they would be considered toxic.

"It's as if the linings of our major organs are hardwired to respond favorably to this elevated level of micronutrients," Dr. Mullin says. "It's pretty remarkable. And relatively untapped." ✨



The goal of work in the lab of James Mullin, PhD, and biomedical research assistant Elizabeth Del Rio is to determine vitamin D's effects to prevent COVID pneumonia.



**WATCH THE VIDEO:**

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## Joining in the fight against autoimmune disease

### SUZI AND SCOTT LUSTGARTEN'S GIFT SUPPORTS KEY INVESTIGATION THAT WILL IMPACT LIVES

**A**s longtime residents of the area, Suzi and Scott Lustgarten are very familiar with Lankenau Medical Center, considering it a valued community resource offering first-class care for cardiac disease and other complex health conditions.

When a family member was recently admitted to Lankenau, the Lustgartens realized how much more the hospital had to offer—and that its medical care was supported by the research and clinical trials of the Lankenau Institute for Medical Research (LIMR).

“I was born at Lankenau,” Scott Lustgarten says. “It is our neighborhood hospital. But then we discovered the depth of the clinical care and the excellence in research, which really piqued our interest.”

They were so impressed that, for the first time, they decided to make a significant philanthropic gift to LIMR, the research division of Main Line Health. They chose to focus on the work of researcher Laura Mandik-Nayak, PhD, an associate professor who is finding new therapeutic strategies to control the progression of autoimmune disorders.

“Autoimmune diseases are complex, debilitating and can take years to diagnose and treat properly,” Suzi Lustgarten says. “This is an area that has been underfunded for years compared to cancer or cardiac research.”

Dr. Mandik-Nayak, an immunologist, became interested in what goes wrong when the immune system attacks itself.



She recognized the need for an approach that focuses on the early stage of autoimmune disease so the underlying mechanisms that activate the immune system can be identified and targeted.

Based on earlier research focused on an enzyme believed responsible for shutting down the immune system of cancer patients, Dr. Mandik-Nayak's lab identified the immunomodulatory enzyme indoleamine 2,3-dioxygenase 2 (IDO2) as a novel molecular player in the initiation and development of autoimmune disease. Recently, her lab demonstrated that loss of IDO2 lowered autoantibody levels and alleviated inflammation in preclinical models of rheumatoid arthritis (RA) and lupus.

Dr. Mandik-Nayak is optimistic that finding a drug to target IDO2 will benefit not only RA patients but those with other autoimmune diseases through a new generation of better therapies with fewer side effects. She has received a grant from the Myasthenia Gravis Foundation to determine if the lessons learned from RA apply to that disease as well.

The Lustgartens have close friends Ann and Rich Frankel to thank for connecting them to LIMR. Regionally, the Lustgartens are committed to pediatric gastrointestinal research and adult colorectal disease, but the Frankels, who are champions for both Lankenau and LIMR, urged Suzi and Scott to learn more about LIMR's research initiatives.

The Frankels recently established an Innovative Research Fund at LIMR to help provide bridge funding for early-stage, pioneering investigations and helped convince Suzi and Scott that innovative research at LIMR would be a meaningful philanthropic opportunity to consider.

“We knew that Suzi and Scott were interested in groundbreaking and state-of-the-art research, so LIMR seemed like a natural fit,” says Rich Frankel, Lankenau Medical Center Foundation Trustee.

“We have always focused our philanthropy on strong medical research in institutions that can make a real difference in people's lives,” Scott Lustgarten says. “We believe Dr. Mandik-Nayak's work will have that kind of impact.” ✨