Main Line Health®

LANKENAU INSTITUTE FOR MEDICAL RESEARCH

CATALYST

FALL 2016

UNLOCKING THE LOST ART OF REGENERATION

Take a medicine and regrow body parts just like an amphibian?
One pioneering LIMR researcher is on a quest to make it possible | Page 2

IN THIS ISSUE

Unlocking the Lost Art of Regeneration | 2

Emerging From the Lab: Pinpoint Delivery of Cancer Therapy | 6

Disarming an Accomplice in Autoimmune Disease | 8

Major Heart Valve Study Comes to Lankenau Medical Center | 11

A Quiet Supporter's Lasting Legacy | 16

LIMR NEWS

- **LIMR embarks on population health research mission** | 14
- **LIMR scientists lead international task force on lethal heart syndromes** | 15

George C. Prendergast, PhD

President and CEO
Lankenau Institute for Medical Research
Main Line Health

WELCOME

What defines us?

At LIMR, we describe our unique research model as *acapreneurial*—a blend of academic science and entrepreneurial biotechnology. Our aim is to make significant scientific discoveries we then turn into medical inventions to improve the lives of people with major diseases.

An extension of our mission and a theme of our work is the study of broad-acting disease modifier pathways such as inflammation and immune response—two common biologic drivers of disease. By themselves, these pathways do not determine the onset but rather the course and severity of disease. For most major diseases, causes can be difficult to precisely define and, thus, treat. But by intervening in the process of disease development, we can favorably alter the outcome and advance health.

LIMR's acapreneurial spirit and disease modifier focus are apparent in the stories ahead. As you will read, regenerative medicine pioneer Ellen Heber-Katz, PhD, came to LIMR to translate her stunning discoveries about mammalian regeneration into medicines that can stimulate human tissue regeneration after devastating loss. Imagine taking a medicine and growing new heart tissue after a heart attack and you get the idea.

In the realm of precision medicine, Janet Sawicki, PhD, and team have devised a novel method to target and eradicate a protein inside ovarian cancer cells that is implicated in promoting growth of the deadly cancer, while bypassing healthy cells. Meanwhile, Laura Mandik-Nayak, PhD, and team have been gaining acclaim for their finding that a disease modifier enzyme discovered at LIMR plays a key role in the development of autoimmune disorders such as rheumatoid arthritis.

In this issue of *Catalyst* you also will learn about a major clinical trial available through Lankenau Heart Institute, which could transform care for many patients with severe aortic valve disease, and about one of our wonderful benefactors, Illa G. Brustman, who left a generous bequest that is helping to support our research efforts.

Since 1927, LIMR's mission has been to advance human health and well-being, and each day this dedication and commitment drives us forward. We hope you enjoy reading about the scientific discoveries and medical advances made possible through your support. ✷

SOMEWHERE ALONG THE EVOLUTIONARY PATH, MAMMALS LOST THE ABILITY TO REGROW BODY PARTS LIKE AMPHIBIANS. OR DID THEY? A LIMR SCIENTIST NOW HAS PROOF THAT MAMMALS NOT ONLY CAN REGENERATE LIKE AN AXOLOTL (PICTURED), THEY CAN DO IT IN MORE THAN ONE WAY.

Unlocking the Lost Art of Regeneration

LIMR professor Ellen Heber-Katz, PhD, is pioneering research to enable mammalian regeneration, having proven that the elusive art is not lost, just locked.

The key to unlocking regeneration may be as simple as a medical treatment. As Dr. Heber-Katz and her collaborators recently showed, giving a precisely aimed drug for a brief time in mice activates regenerative healing rather than wound repair (scarring) after injury. If this approach works in humans, it could open a world of opportunity to restore function after devastating disease or loss.

Remarkably, this promising pathway to regeneration might have gone unnoticed had Dr. Heber-Katz not stopped what she was doing to investigate something funny going on in her lab.

The case of the vanishing ear holes

In 1995, Dr. Heber-Katz was doing an autoimmunity study in MRL mice when she noticed that the small holes punched in the animals' ears quickly refilled rather than healing open as usual. (The MRL mouse strain is used in autoimmunity research, and ear holes help distinguish mice during a study.)

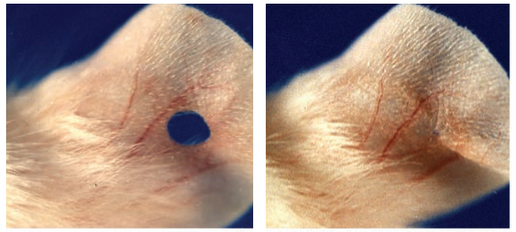
Thinking she'd stumbled on a clue to rapid wound healing, she consulted another scientist, who said it looked more like regeneration than normal healing.

"Regeneration!" exclaims Dr. Heber-Katz. "I had no idea what that was, but I was determined to know what was going on."

Against her colleagues' advice, Dr. Heber-Katz jumped into the field of regenerative biology and set out to solve the mystery of the vanishing ear holes, leaving a successful career in immunology research behind. Over the next 2 decades, her work earned her international recognition as a trail blazer and leading authority in the study of mammalian regeneration. In 2014, Dr. Heber-Katz came to LIMR to lead the Laboratory of Regenerative Medicine and begin studies aimed at translating her scientific findings into a useful medicinal tool.

Swimming against the tide

At the time Dr. Heber-Katz began her quest, most scientists believed that amphibians were the last branch of the evolutionary tree able to regrow lost or injured tissues and that mammals, with few exceptions, could only repair wounds with a scar.



Dr. Heber-Katz's scientific investigation of mammalian regeneration was sparked when she discovered this: a hole punch made in the ear of an MRL mouse (left) disappeared in just 1 month (right).

"There were two camps—regeneration scientists who studied amphibians, and wound-healing scientists who studied mammals," she explains. "The two groups didn't interact because no one believed mammals could regenerate."

Realizing she was in uncharted territory, Dr. Heber-Katz engaged a network of collaborators in an intensive study of the MRL mouse. The researchers found that the mouse not only could regrow skin, cartilage, and hair follicles to refill ear holes, it could grow new heart muscle, nerves, and parts of fingers and toes.

With evidence of body-wide regeneration, Dr. Heber-Katz turned to finding the basis for the animal's healing response.

Unraveling the mystery of the regenerating mouse

The search for clues to the MRL mouse's regenerative ability has been a long adventure filled with discoveries. "We saw something new every day," says Dr. Heber-Katz.

The researchers noticed that the adult MRL mouse has features more like an embryo. The animal continues to grow, becoming very large and fat. It also has an unusual metabolism, using aerobic glycolysis for cellular energy production, similar to a developing embryo.

When the researchers examined cells from MRL mouse ear holes, they found that the cells multiplied quickly compared to cells from nonregenerating mice. MRL mouse cells also were *dedifferentiated*, meaning they reverted to an immature stage, displaying a host of stem cell markers.

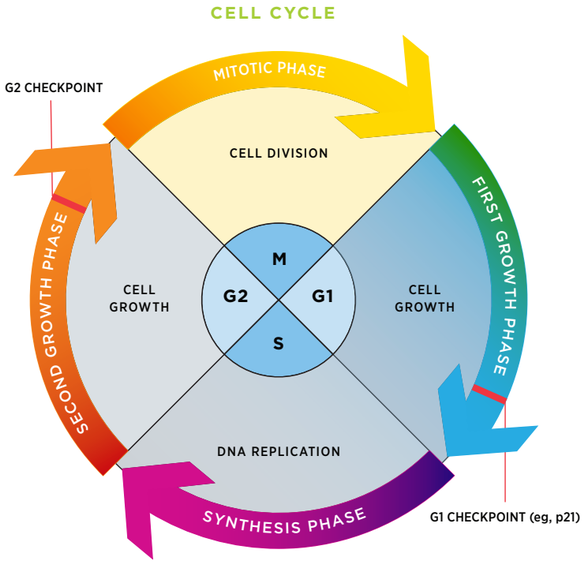
Then, an analysis of the cell cycle revealed something surprising—large peaks in the G2 phase of the cycle (after DNA replication but before cell division), indicating that many cells were accumulating there, as if they were stopped to repair DNA damage.

"This made no sense," notes Dr. Heber-Katz. "How could the cells multiply so quickly when so many were in G2?" More perplexing, the cells showed extensive DNA damage. This led the researchers to look at *checkpoint molecules* that stop cells from dividing when DNA damage is detected. The first molecule examined was p21. Bingo!

"It turns out the p21 protein is missing in MRL mice," says Dr. Heber-Katz. To test that absence of p21 can activate regeneration after injury, the researchers punched ear holes in mice genetically engineered to lack the p21 gene (called *knockout mice*) and then watched. "Sure enough, we saw fantastic regeneration," she says.

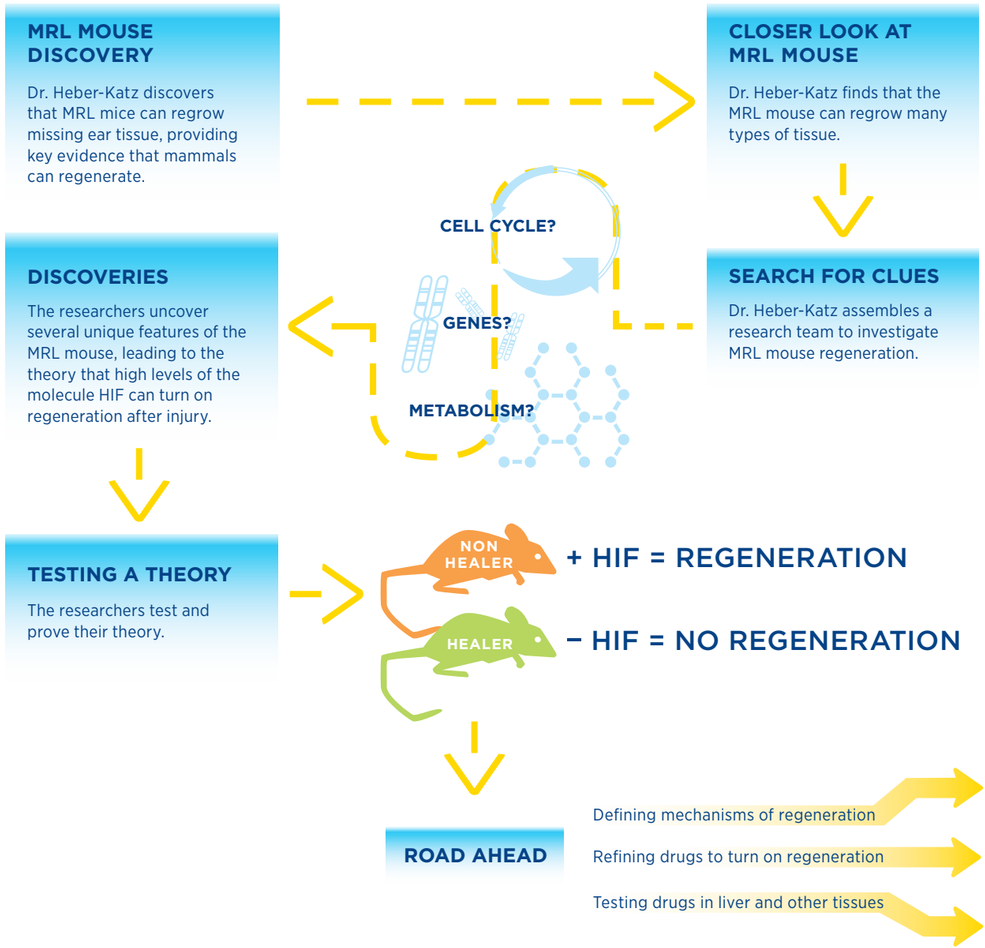
A picture started to form when the researchers looked at another molecule called *hypoxia-inducible factor* (HIF). Because MRL mice use a metabolism regulated by HIF (aerobic glycolysis), HIF was an obvious suspect. Furthermore, HIF can downregulate p21, so if p21 is low or absent, there could be higher levels of HIF in cells.

"Indeed, we found that HIF increases early during the regenerative response in MRL mice, then it starts to come down," notes Dr. Heber-Katz. "Everything pointed to HIF and p21 being key regulators of regeneration."



Most living organisms undergo a continuous four-phase process of cell growth and division called the cell cycle. This process is tightly regulated by internal checkpoint molecules that halt progression to the next phase if a problem is detected.

CONTINUED ON NEXT PAGE



Proving a hunch

A major breakthrough came when the researchers did a two-way test of their theory that high HIF levels at the time of injury trigger regeneration.

- **Test 1.** First, they did an ear hole punch in mice that cannot regenerate and gave a drug to increase HIF, which resulted in complete ear hole closure similar to that seen in MRL mice.
- **Test 2.** Then, they did an ear hole punch in MRL mice and used a genetic tactic to block HIF. This time, the mice did not respond with regenerative healing.

"Drug-induced regeneration happened fast," says Dr. Heber-Katz. "In 1 month, the effect was complete. All we had to do was increase HIF for 10 days."

Examining the process at the cellular level, she notes, "When we added the drug, raising HIF, we saw dedifferentiation of mature cells into an immature state where the cells could then proliferate. When we stopped the drug, lowering HIF, we saw the cells redifferentiate into skin, cartilage, and hair follicles."

This type of regeneration, called *epimorphic regeneration*, is used by the axolotl and other amphibians.

The HIF mouse study was completed shortly before Dr. Heber-Katz joined LIMR and was published in 2015 in *Science Translational Medicine*. As LIMR president George Prendergast, PhD, points out, the regeneration approach is novel in that it is not based on transferring stem cells. He notes that stem cells can be hard to control in patients who receive them, sometimes growing the wrong way, dying out early, or even posing risks of cancer.

"Dr. Heber-Katz's team found a way to turn on regeneration at the site of injury without stem cells," says Dr. Prendergast. "This unique approach required only a brief targeted treatment to spark appropriate tissue regrowth. The potential clinical implications of this approach are enormous, especially the prospect for an off-the-shelf regenerative medicine that might be able to treat any patient."

The road ahead

Since arriving at LIMR, Dr. Heber-Katz has forged new collaborations that are spurring her work forward.

"I couldn't ask for a more stimulating or supportive research environment than LIMR," she says. "Turning discoveries into meaningful medical interventions is a mission here."

She and her collaborators are pursuing several new paths of research. "We've found another gene linked with regeneration, which we're excited to study," she says. "We're also optimizing the HIF study drug, developing new drugs to kick start regeneration, and testing the drugs in other tissues."

Dr. Heber-Katz is working with LIMR's Janet Sawicki, PhD, to develop a new drug approach using nanoparticle technology. As for tissue studies, she and long-time collaborator Phillip Messersmith, PhD, of the University of California at Berkeley, are testing the effect of HIF-activating drugs on jaw bone and periodontal ligament damage in mice. These studies have been funded by a grant from the National Institute of Dental and Craniofacial Research at the National Institutes of Health, which recognized the special implications of the research in this area.

Regeneration studies in liver and other tissues

"We're also keen to test a drug approach to regrowing cartilage, heart tissue, and liver tissue," Dr. Heber-Katz says, although these studies are not yet funded. A liver study is being planned that would involve collaboration with a Thomas Jefferson University transplant surgeon and a surgical resident currently working in the Heber-Katz lab.

It may come as a surprise to test the liver, since it is the rare human organ that can regenerate. But normal liver regeneration may fall short in restoring life-sustaining function in patients with advanced liver disease.

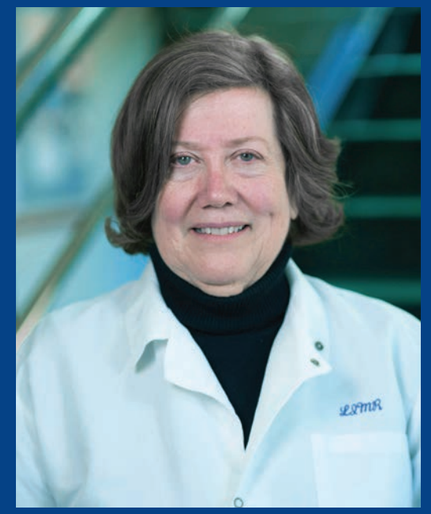
"The implications of being able to regenerate liver tissue are tremendous," says liver specialist Scott Fink, MD, Chief of Hepatology at Main Line Health. "It would revolutionize treatment of advanced liver disease if patients with acute liver failure or cirrhosis could regain their own liver function."

As Dr. Fink explains, when a person's liver is damaged beyond repair, the only life-saving option is liver transplantation. "But if that patient's liver could fully regenerate, recovery could be hastened and the risks and complications of transplantation could be avoided."

Dr. Heber-Katz hopes to secure funding to move ahead with the liver study. She says the goal is to test the drug used in the HIF study and nanoparticle therapy in mice that have undergone extensive liver resection to see if either treatment or both can induce regeneration and restore normal liver function.

As she excitedly adds, "Wouldn't that be wonderful!"

SNAPSHOT



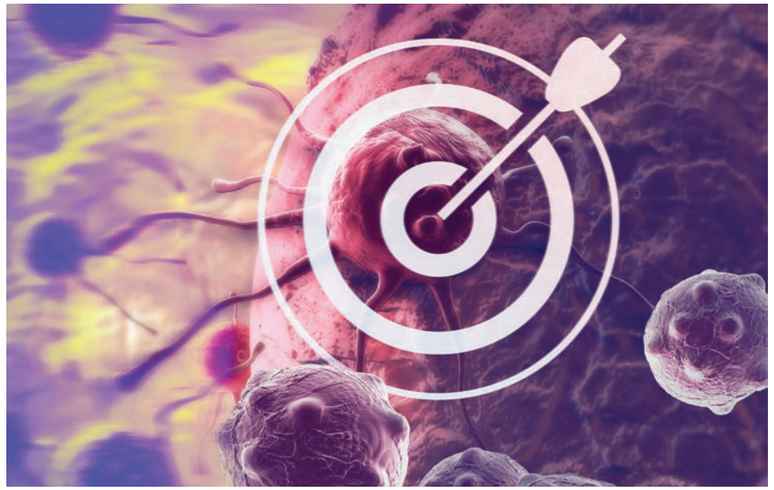
Ellen Heber-Katz, PhD
Professor, Laboratory of Regenerative Medicine, LIMR

BACKGROUND AND RESEARCH FOCUS

Dr. Heber-Katz is an internationally recognized scientist whose explorations span the fields of immunology, vaccines, wound healing, and regeneration. Following postdoctoral work at the National Institutes of Health, she joined The Wistar Institute, where her study of autoimmunity led to the discovery of a mouse capable of spontaneous tissue regrowth similar to the type of regeneration seen in amphibians. After unraveling the biologic basis for this phenomenon and proving drug-induced regeneration is possible, Dr. Heber-Katz moved to LIMR to begin research in mammalian regeneration aimed at developing a useful medicine.

FUN FACT

Sings while doing experiments.



PRECISION MEDICINE HAS TAKEN A GREAT LEAP FORWARD IN THE LIMR LAB OF JANET SAWICKI, PHD, WHO, WITH HER COLLABORATORS, HAS DEVISED A NOVEL METHOD TO TARGET AND ERADICATE CANCER CELLS WHILE BYPASSING HEALTHY CELLS.

Emerging From the Lab: Pinpoint Delivery of Cancer Therapy

Precision medicine has the potential to significantly improve cancer treatment. The strategy is simple in principle: identify specific proteins or genetic abnormalities that drive tumor development, then design therapies to target them. Executing that strategy is anything but simple.

LIMR professor and deputy director Janet Sawicki, PhD, and colleagues have teamed up with scientists at Genisphere LLC, a biotech company, to develop and test an innovative approach to precision cancer treatment using Genisphere's nanocarrier drug-delivery method called 3DNA® technology. The research consortium's promising early results with the approach were published earlier this year in *Cancer Research*.

First target: lethal ovarian cancer cells

The sobering facts about ovarian cancer were the backdrop for the research team's first test of 3DNA technology. Ovarian cancer causes more deaths than any other gynecologic cancer. One reason is late diagnosis; another is the cancer's stubborn drug resistance.

The asymptomatic nature of early ovarian cancer and lack of effective screening techniques result in most patients being diagnosed after the disease has spread beyond the ovary.

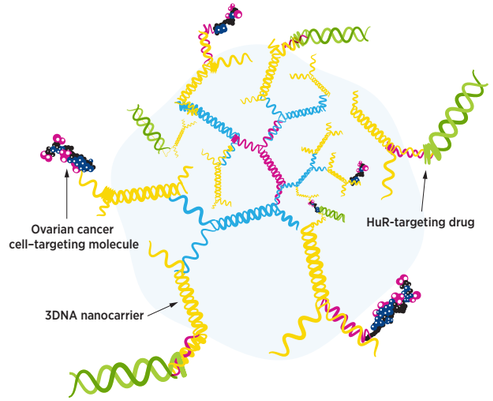
Although patients usually respond to initial treatment, the cancer typically recurs because tumor cells develop drug resistance. Unfortunately, the 5-year survival rate for patients with distant metastases is only 27%.

The research team used an animal model of ovarian cancer to test 3DNA technology. The aim was to target HuR, a protein found in high amounts in ovarian tumor cells and strongly linked with cancer development and progression.

HuR regulates hundreds of genes that function in critical molecular pathways needed for tumor cell survival. During times of cellular stress (eg, exposure to chemotherapy), it's believed that HuR enables the most aggressive cancer cells to survive. Stopping HuR from wreaking cellular havoc, while leaving healthy cells intact, was the goal of the study.

HuR-targeting strategy

Using 3DNA technology, the researchers were able to deliver small interfering RNA (siRNA)—an established molecular technique that inhibits function of a single gene—directly to ovarian tumors in mice, with great results. Targeted HuR inhibition greatly reduced tumor growth rate, significantly extended life span, and caused no harm to healthy cells.



3DNA® technology is a versatile nanocarrier drug-delivery molecule with multiple arms. Researchers can attach a variety of drugs to the arms to target specific tumors and direct uptake of the drugs by those tumors.

Dr. Sawicki notes that delivery of siRNA to tumors via typical drug administration routes—infusions, injections, or pills that enter the bloodstream—has been a major challenge impeding advancement of promising siRNA-based therapies. "3DNA nanocarrier technology meets that challenge," she says. One reason is that the nanocarrier is designed to shield the siRNA drug cargo from the harsh physical environment found in body fluids and tissues.

Think of it like NASA's Juno spacecraft that entered Jupiter's orbit in July, after a years'-long journey. NASA likened the success of the Juno mission to hitting a golf ball in New York and landing a hole in one in Los Angeles.

3DNA technology carries a cancer therapy through the vast expanse of a patient's bloodstream and then—in pinpoint fashion—delivers the drug to the exact tumor location, bypassing and leaving intact healthy cells along the route.

Because HuR regulates hundreds of genes, targeted inhibition of HuR has a wide range of effects leading to tumor cell death. Dr. Sawicki points out that, in addition to inhibiting tumor growth, suppressing HuR is likely to combat development of drug resistance by tumor cells and, thus, decrease the likelihood of tumor recurrence.

"This work takes a major step forward in the field of cancer siRNA therapeutics and advances the potential use of 3DNA technology to the clinical setting," says Dr. Sawicki. "If we can overcome drug resistance and extend overall survival in ovarian cancer, we can likely modify the technology for use against other tumor types with similar positive consequences."

In addition to Dr. Sawicki, other LIMR-affiliated members of the research consortium included Yu-Hung Huang, PhD; Weidan Peng, PhD; and Narumi Furuuchi. The group also included scientists from Thomas Jefferson University's Department of Surgery; the Max Delbrück Center for Molecular Medicine in Berlin, Germany; and Seattle-based NanoString Technologies, a provider of life science tools. The work was funded in part by grants from private foundations, including the Marsha Rivkin Center for Ovarian Cancer Research, the Sharpe-Strumia Research Foundation of Bryn Mawr Hospital, and the Sarah Parvin Foundation.

New targets and next steps

Dr. Sawicki notes that the now-proven nanocarrier drug-delivery method potentially could be used to treat cancers of the pancreas, lung, colon, prostate, and breast, as well as glioblastomas (brain tumors) and lymphomas.

"Different tumor types display different molecules on the surface of cancer cells, and using the technology, we can modify the nanocarrier to deliver treatment to specific cancer types, thus enabling custom-made cancer therapy," says Dr. Sawicki.

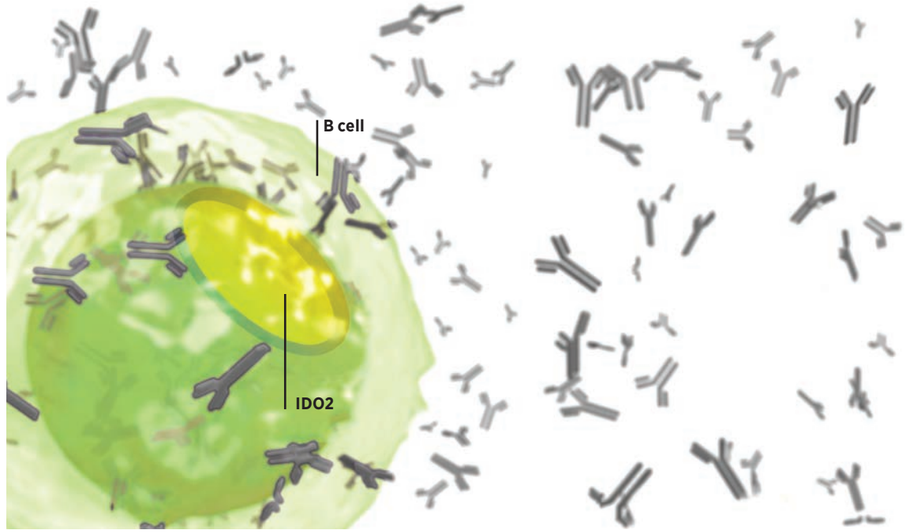
The nanocarrier approach can also be used to target traditional chemotherapy to tumors. As Dr. Sawiki explains, "3DNA technology allows us to reduce the deleterious effects of chemotherapy to healthy cells. We can reduce the dosage, which in turn reduces the off-target toxicity typical of chemotherapeutic agents."

This year, the researchers expanded their studies to pancreatic cancer, and they hope to include glioblastomas next. "The therapy is the same, but we're targeting it differently," says Dr. Sawicki. The team currently is seeking funding for these next steps in research.

As for the team's ovarian cancer research, the ultimate goal is to begin phase 1 clinical trials, which would be the first with 3DNA technology, in patients who have advanced ovarian cancer with recurring tumors.

"If we can overcome drug resistance and extend overall survival in ovarian cancer, we can likely modify the technology for use against other tumor types with similar positive consequences."

— Janet Sawicki, PhD



NO ONE KNOWS WHY THE IMMUNE SYSTEM SOMETIMES TURNS AGAINST THE BODY, BUT A LIMR TEAM HAS IDENTIFIED AN ENZYME THAT ENABLES THE MISGUIDED ATTACKS. NOW THE TEAM IS WORKING ON STRATEGIES TO BLOCK THE ENZYME AND OPEN NEW AVENUES FOR TREATING AUTOIMMUNITY.

Disarming an Accomplice in Autoimmune Disease

The immune system usually gets it right, distinguishing bad guys from the body's billions of microscopic parts and targeting only true troublemakers for attack. This delicate balance of immune response (to nonself) and immune tolerance (to self) relies on precise coordination across the system and perfect teamwork by two key groups of cells: T cells and B cells.

But the system can falter and immune tolerance can break down, allowing autoreactive immune cells to become activated and mount an attack on healthy cells or tissues. While this is the recognized basis of autoimmune disease, the mechanisms involved in starting an autoimmune response are largely unknown.

LIMR immunologist and associate professor Laura Mandik-Nayak, PhD, has been leading an investigation to uncover factors driving the inflammatory autoimmune response in rheumatoid arthritis (RA) and systemic lupus erythematosus (lupus)—two progressive and debilitating diseases with no cure. The investigative work, which involves mouse models of RA and lupus, began before Dr. Mandik-Nayak joined LIMR in 2006 and has now matured to the point of hinting at answers she has been seeking.

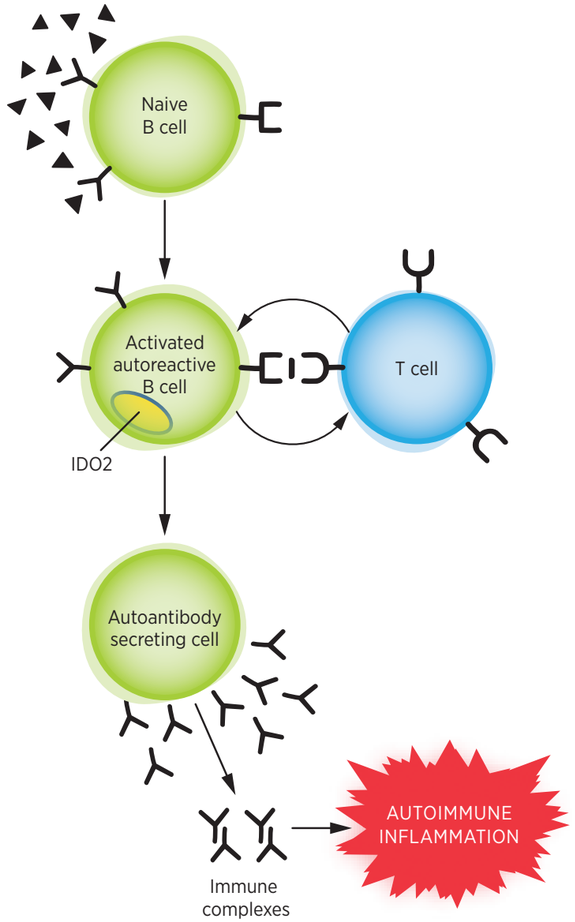
How does autoimmune disease happen?

"I've always been interested in how immune tolerance breaks down," says Dr. Mandik-Nayak. "Why are we able to mount an autoimmune response at all? Why aren't autoreactive cells controlled in everyone? How do immune responses against self proteins get started and propagate, and how can this activity be turned off?"

When Dr. Mandik-Nayak joined LIMR, Alexander Muller, PhD, and George Prendergast, PhD, were studying IDO1, an enzyme implicated in immune regulation, and its effects in cancer. This sparked Dr. Mandik-Nayak's interest to investigate connections between the IDO enzyme pathway and inflammatory autoimmune disease.

"If you think about it, cancer and autoimmunity are like two sides of a coin," she says. "In cancer you are not getting an immune response that you want, and in autoimmunity you are getting an immune response that you do not want."

Another reason for her interest in IDO is that the enzyme breaks down tryptophan, and blood tests in patients with autoimmune disease show high levels of tryptophan breakdown products, suggesting a key role for the IDO pathway.



A major focus of Dr. Mandik-Nayak's autoimmunity research is IDO2, an enzyme her research has implicated in activating autoreactive B cells. Once activated, autoreactive B cells begin secreting autoantibodies that mount an attack against healthy tissues in the body. Dr. Mandik-Nayak is looking to determine exactly how IDO2 is working inside B cells to disrupt normal communication with T cells. With LIMR associate professor Dr. Lisa Laury-Kleintop, she also is exploring ways to block the action of IDO2 to reduce inflammatory damage in rheumatoid arthritis, lupus, type 1 diabetes, and other autoimmune diseases.

Drs. Muller and Prendergast were using a drug to turn off IDO in mouse models of cancer after learning that tumors turn on the enzyme pathway to suppress an immune response. Dr. Mandik-Nayak theorized that using the same drug in autoimmune disease would make the disease worse if IDO was involved. In fact, it did the opposite: the IDO-blocking drug alleviated arthritis in the mice being studied.

"My first thought was that we did something wrong," she says. "But after repeating the experiment with the same result, we knew we had to investigate."

Dr. Mandik-Nayak's group discovered that the IDO inhibitor alleviated arthritis by lessening an autoreactive B cell response. Their published report was the first to link IDO with stimulation of autoreactive B cells. Clearly more was going on in the IDO pathway than just the immunosuppression seen in cancer studies.

Knowing autoreactive B cells play a central role in RA, Dr. Mandik-Nayak wondered what adding an IDO inhibitor to standard RA therapy might do. She and her collaborators decided to try the IDO blocker in combination with methotrexate (a drug that inhibits the inflammatory response) and rituximab (a drug that temporarily wipes out B cells to "reboot" the immune system).

"When we added the IDO inhibitor to methotrexate, there was a synergistic effect, so much that we could lower the methotrexate dose and still get a big benefit," she says. When the researchers gave the IDO inhibitor after knocking out B cells with rituximab, rather than seeing a spike in RA when B cells returned, the disease remained quiet.

"These studies showed us early on that IDO holds promise as a target for RA cotherapy," Dr. Mandik-Nayak notes, adding, "IDO inhibitors may not replace current therapies, but they could make them work better or allow you to use less of them, reducing potential side effects."

Digging deeper into the IDO pathway

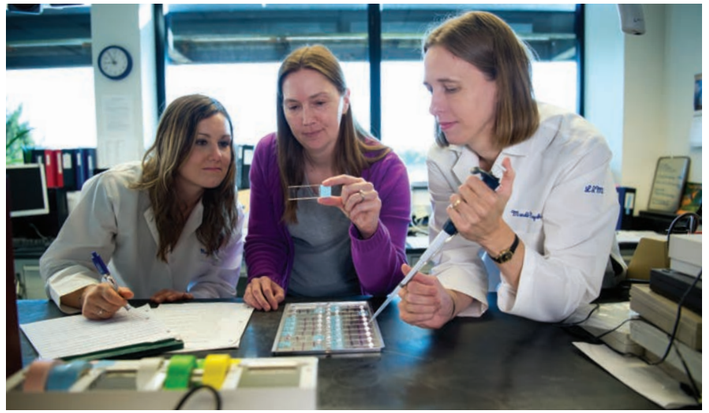
The subsequent LIMR scientists' discovery that the IDO pathway involves a second enzyme, IDO2, opened a new vista of exploration for Dr. Mandik-Nayak's group, which since 2011 has included research assistant professor Lauren Merlo, PhD.

"We became interested in looking at each enzyme, but particularly what IDO2 might be doing in autoimmunity," says Dr. Merlo. "The distinction between IDO1 and IDO2 is important, as the two enzymes play fundamentally different roles during immune responses."

To tease out what each enzyme is doing, the researchers studied mice genetically engineered to lack either IDO1 or IDO2 (called *knockout mice*).

An intensive investigation of the role of IDO2 in autoimmune disease culminated in two major reports in *The Journal of Immunology* in 2014 and 2016. The work involved experiments comparing mice with IDO2 to IDO2 knockout mice, with the aim of identifying which immune system players used IDO2 to mediate the autoimmune response.

CONTINUED ON NEXT PAGE



Dr. Mandik-Nayak (center) with research team members Dr. Merlo (right) and Samantha Grabler (left). The team is working to identify factors driving an autoimmune response in inflammatory diseases such as rheumatoid arthritis and lupus.

AUTOIMMUNE DISEASES THAT INVOLVE B CELLS

DISEASE	TARGET OF INFLAMMATORY DAMAGE
Rheumatoid arthritis	Joints
Lupus	Whole body
Type 1 diabetes	Insulin-secreting cells of the pancreas
Celiac disease	Small intestine
Hashimoto's thyroiditis	Thyroid gland

"We tested this idea with a series of cell transfer experiments," says Dr. Merlo. "Basically, we took mice that were missing components of their immune system, added different immune cell types back, and showed that the presence or absence of IDO2 in the B cells really mattered in inducing arthritis."

The researchers discovered that IDO2 is at work inside the B cell, driving the cell's autoreactive response that leads to arthritis. Further, IDO2 appears to specifically affect the production of tissue-damaging autoantibodies, not all antibody responses in general. This disease selectivity suggests that autoreactive responses could be blocked without harming protective responses.

Dr. Mandik-Nayak acknowledges that her lab has helped define the importance of distinguishing between IDO1 and IDO2 when studying the IDO pathway. "We've shown that IDO1 and IDO2 are doing different things and probably acting in different cell types," she says, adding that her lab is currently leading the way in looking at IDO2 in autoimmunity.

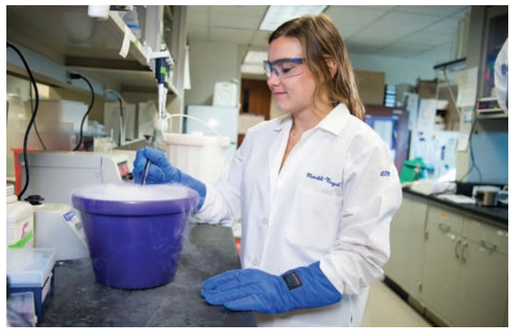
Exploring new opportunities for autoimmunity treatment

While the Mandik-Nayak lab continues to look at what exactly IDO2 is doing in autoimmune disease, proof of IDO2 involvement opens the door to investigating potential treatments to block the action of the enzyme.

"We're working on ways to target IDO2 without hitting IDO1, with the goal to find a strategy that can translate into treatment to help people with autoimmune disease," says Dr. Mandik-Nayak. She says a lead drug candidate developed by LIMR colleague Lisa Laury-Kleintop, PhD, is producing promising, soon-to-be-published results in animal models of RA and lupus as well as type 1 diabetes.

Dr. Mandik-Nayak is hopeful her team's findings offer clues to reducing inappropriate immune cell activity in a range of autoimmune disorders. "Because IDO2 appears to act at the initiation of an immune response, we believe it is probably involved in other autoimmune diseases," she says.

IDO research in the Mandik-Nayak lab at LIMR has been supported by grants from the National Institutes of Health and the Zuckerman Family Autoimmune Disorder Research Fund. A grant from the Lupus Research Institute is helping fund investigation of IDO2 in lupus.



LANKENAU HEART INSTITUTE'S STELLAR TEAM FOR TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) WAS HANDPICKED FOR A NEW NATIONWIDE CLINICAL STUDY OF TAVR.

Major Heart Valve Study Comes to Lankenau Medical Center

Lankenau Heart Institute's TAVR program has been chosen to participate in PARTNER 3, a nationwide clinical trial that could transform the treatment of severe aortic stenosis.

The study focus is TAVR, a catheter-based therapy that has proved to be a safe and effective alternative to surgical aortic valve replacement (SAVR) in people at moderate or higher risk for undergoing heart surgery. PARTNER 3 is the first large randomized clinical trial in the U.S. to assess whether these benefits also translate to patients at low risk for surgery.

"The answer to this question could profoundly change treatment for many people suffering from aortic stenosis," says interventional cardiologist Paul Coady, MD, Lankenau Heart Institute's principal investigator for PARTNER 3.

As Dr. Coady explains, if TAVR results are positive, TAVR could become the main treatment for severe aortic stenosis, with SAVR a secondary approach. Physicians need solid proof that TAVR is as good or better, which the study is designed to provide.

Lankenau Heart Institute's TAVR program, based at Lankenau Medical Center, is one of the few programs chosen to participate in PARTNER 3 that was not part of the original PARTNER study group. Dr. Coady credits the successful efforts of the team's dedicated surgeons, interventional cardiologists, echocardiographers, and nurse coordinators with their selection for PARTNER 3.

"We're gratified to contribute to this important research," he says, speaking on behalf of Lankenau Heart Institute's specialized team for structural heart disease. He says the team has worked hard to build a robust TAVR program, which has grown substantially since its launch in 2012.

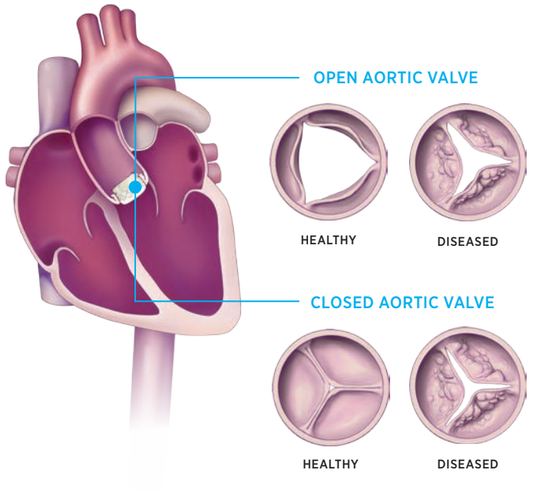
"We completed 500 TAVR procedures by the time we hit our 4-year program anniversary in 2016," Dr. Coady reports. "And we're proud of the excellent patient outcomes we've achieved."

Easing the burden of aortic stenosis: a role for TAVR?

Aortic stenosis usually develops later in life and causes no symptoms until it has progressed to the point that the aortic valve is failing. Once symptoms start, the risk of sudden death is high—up to 50% of untreated patients die within 2 years of symptom onset. Symptomatic aortic stenosis can only be improved by replacing the aortic valve.

Because valve replacement eases symptoms and adds healthy years of life, it is recommended for most patients with severe aortic stenosis. Yet, many patients who would benefit from the treatment do not undergo aortic valve replacement.

CONTINUED ON NEXT PAGE



Aortic stenosis is a narrowing of the valve that opens to let blood flow from the heart to the rest of the body. The disease most often is caused by age-related buildup of calcium. As the valve opening narrows, the heart must work harder to supply blood, leading to symptoms and a rapid downhill course. An estimated 2.5 million people in the U.S. over the age of 75 suffer from aortic stenosis.

"One reason PARTNER 3 is important is because if it shows TAVR is safe and effective in low-risk patients, it could help break down barriers to treatment," says cardiac surgeon Scott Goldman, MD, surgical leader of Lankenau Heart Institute's Structural Heart Program.

Studies show that only about 50% of patients with severe aortic stenosis are referred for valve replacement. Reasons include patients not reporting symptoms or mistaking them as a normal part of aging and patient or physician reluctance to consider heart surgery.

"SAVR actually is a very safe procedure," notes Dr. Goldman. "Over the past 12 months at Lankenau Medical Center, we have had no deaths related to SAVR." On average, about 150 SAVR procedures are performed each year at Lankenau Medical Center, nearly all of which are done minimally invasively.

SAVR also is effective. But as Dr. Goldman acknowledges, surgery has risks. Because of these risks, some people had no option for valve replacement before TAVR became available. Now, TAVR is increasingly taking the place of SAVR in high-risk patients.

Besides opening the door to treatment, TAVR offers benefits to patients, says Dr. Goldman. As he explains, "The procedure is mostly done under local anesthesia and involves little down time, which should make TAVR more appealing to patients needing aortic valve replacement."

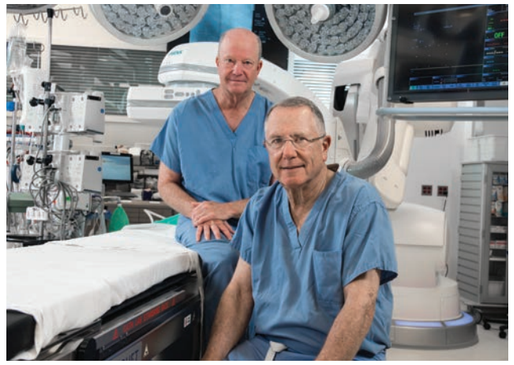
Dr. Goldman hopes that raising awareness of a potential low-impact option will lead to treatment of more patients. "This is important," he says, "because untreated severe aortic stenosis is worse than any treatment we have, surgical or TAVR. Any way we can get these patients treated is good."

Goals and design of the PARTNER 3 study

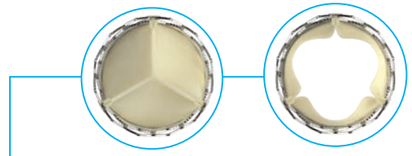
The aim of PARTNER 3 is to determine the safety and effectiveness of TAVR using the SAPIEN 3 heart valve in patients requiring aortic valve replacement and at low operative risk for SAVR. Initially approved for use in high-risk patients, the SAPIEN 3 valve was recently approved for patients at moderate risk for surgery based on positive results of SAPIEN 3 TAVR compared to SAVR.

In PARTNER 3, more than 1,200 qualified low-risk patients with symptomatic aortic stenosis will be enrolled and randomly assigned to treatment with TAVR or SAVR. Enrollment by Lankenau Heart Institute's TAVR team began in September 2016 and is occurring at Lankenau Medical Center. At Lankenau, a PARTNER 3 patient who is randomized to SAVR will be evaluated for and, if a candidate, offered minimally invasive SAVR.

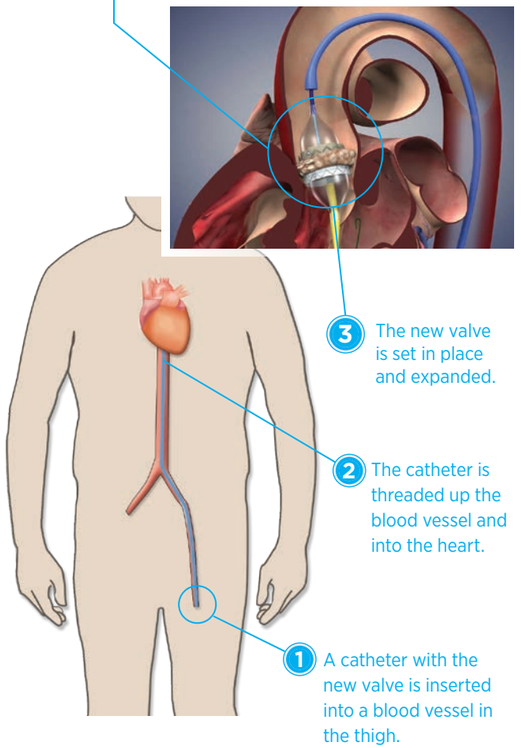
PARTNER 3 will compare rates of death, stroke, and rehospitalization 1 year after TAVR versus SAVR. The researchers will then monitor study patients to compare outcomes of the two therapies over several years.



For years, Dr. Coady (left) honed cardiac interventional expertise in the catheterization lab while Dr. Goldman (right) developed minimally invasive cardiac surgical expertise in the operating room. Now, the specialists work side by side in a multidisciplinary heart valve team.



The SAPIEN 3 valve, shown closed (left) and open (right), is made of cow heart tissue sewn into an expandable frame (stent).



TAVR (transcatheter aortic valve replacement) allows a diseased aortic valve to be replaced without heart surgery. The most common approach to TAVR is to implant the new valve by way of a catheter (thin tube) that is inserted into a blood vessel in the thigh.

Dr. Coady notes that while PARTNER 3 is focused on treatment of severe aortic stenosis, the goal of clinical research is always the same.

"Whether it's heart disease, cancer, or another disease, the aim is to find the safest, most effective, and most long-lasting therapies for patients," he says. "This is the opportunity PARTNER 3 offers—to be able to say to patients that either TAVR or SAVR is the safest way we can treat them to get the best outcome for the longest period of their lives. That's why this study is so important."

ALSO FROM LANKENAU HEART INSTITUTE

New device tested in peripheral artery disease

Peripheral artery disease is a narrowing or blockage of blood vessels that supply the legs. Fatty deposits build up inside the arteries, restricting blood flow and causing leg pain and other symptoms, especially during walking or exercise. As peripheral artery disease worsens, symptoms may occur at rest. The condition is common and can be serious.

Angioplasty is a procedure to open blood vessels affected by peripheral artery disease. Unfortunately, blood vessels tend to clog again. To combat this, stents (tiny scaffolds) are used to help keep vessels open after angioplasty treatment. Stents have evolved to be more effective, and one approach is a stent that slowly releases a drug to prevent new blockages. Only one device of this type, the Zilver® PTX® stent, has been approved for use in the U.S. in patients with severe peripheral artery disease.

A second device, the ELUVIA™ drug-eluting vascular stent system, is being tested against the Zilver PTX stent in a randomized clinical trial available through Lankenau Heart Institute. Intended for above-the-knee peripheral artery disease, the ELUVIA stent system is designed to prevent reblockage after an angioplasty procedure.

The aim of the IMPERIAL study, which will enroll patients at sites worldwide, is to evaluate the safety and effectiveness of the ELUVIA stent system compared to the Zilver PTX stent. Interventional cardiologist Antonis Pratsos, MD, is principal investigator for the Lankenau Heart Institute study site.

The global principal investigator for the IMPERIAL study is Lankenau Heart Institute president and Main Line Health system chief of cardiovascular disease William Gray, MD.

To learn more about LIMR clinical trials conducted by Lankenau Heart Institute, go to:

mainlinehealth.org/research/clinical-trials/cardiac

Updates from LIMR Principal Investigators

Susan Gilmour, PhD, LIMR professor, was elected by her scientific peers to chair the 2017 Gordon Research Conference on Polyamines. The leadership role is a significant honor, as this biannual conference will provide an opportunity to showcase major polyamine discoveries by scientists from around the world. Polyamines—small organic compounds found in all cells—are closely linked to cancer cell growth, survival, and proliferation.

Scott Dessain, MD, PhD, LIMR associate professor, has co-authored *Preserving the Promise: Improving the Culture of Biotech Investing* (Academic Press). The new book examines why so many medical discoveries never reach the point of being translated into medicines and offers practical alternatives for improving the development process.

Charles Antzelevitch, PhD, LIMR professor, has received the 2016 Douglas P. Zipes Lectureship Award from the Heart Rhythm Society. The annual award is given to an individual who has made a significant and unique contribution to the field of cardiac pacing and electrophysiology as a basic scientist.

Melvin Reichman, PhD, LIMR senior investigator, was named president of the International Chemical Biology Society (ICBS) for a second term. ICBS is an independent nonprofit organization dedicated to promoting drug-discovery research and educational opportunities at the interface of chemistry and biology.

LIMR Embarks on Population Health Research Mission

LIMR's research focus has expanded into the realm of population health—a vital scientific field devoted to examining the social determinants and other forces that define the health and well-being of populations.

In August, LIMR partnered with a pioneer in the field, Jefferson College of Population Health (JCPH), to launch the Population Health Research Center, the mission of which is to conduct research that sheds important light on issues impacting effective population health management.

The Center will spearhead studies exploring the unique needs and characteristics of the diverse populations served by Main Line Health, including research that will help the organization enhance current care models and outcomes through a better understanding of the social and economic challenges inherent or under-addressed in the community.

LIMR president and CEO George Prendergast, PhD, underscores the important role the new Population Health Research Center will play. "The Center will help us close care gaps and address disparities in health across the community, including those that are not fully understood or even identified yet," says Dr. Prendergast. "We look forward to furthering our expertise in this important field of research."

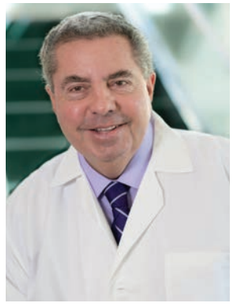
David Nash, MD, MBA, founding dean of JCPH, adds, "We are breaking new ground by creating a nationally visible research center focused on population health. The research we conduct here will directly influence and inform the delivery of health care on a local, regional, and national level."

LIMR welcomes Norma Padrón, PhD, MPH, as associate director of the newly formed Population Health Research Center.

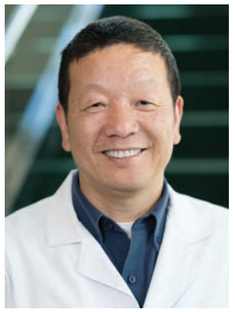
Norma Padrón, PhD, MPH, has been named associate director of the Center. Previously an assistant professor of health economics at the Icahn School of Medicine at Mount Sinai in New York City and a health economist at the New York Academy of Medicine, Dr. Padrón will work with Main Line Health clinicians and researchers as well as JCPH faculty to develop a robust research agenda for the Center.

"I look forward to building the new program into one that offers comprehensive and relevant data and evidence to the research community—research that can help improve well-being and quality of life for people in our region and across the country," says Dr. Padrón.

LIMR Scientists Lead International Task Force on Lethal Heart Syndromes



Charles Antzelevitch, PhD



Gan-Xin Yan, MD, PhD

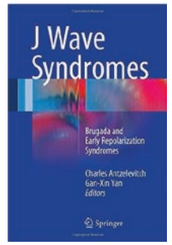
LIMR cardiac researchers Charles Antzelevitch, PhD, and Gan-Xin Yan, MD, PhD, and their international colleagues have developed and published the first clinical consensus report on a group of life-threatening heart conditions known as *J wave syndromes*.

Although J wave syndromes might not ring a bell, most people are aware of the tragedy of sudden cardiac arrest in a young, previously healthy person. As heart specialists work to understand what causes these tragic events, one thing is clear: J wave syndromes play a significant role.

J wave syndromes get their name from the J wave, which is one of the waves in an electrocardiogram (ECG). Long thought to be harmless, accentuated J waves are now known to be linked with increased risk for sudden cardiac death. Still, there is considerable confusion across the medical community about how to properly diagnose and treat J wave syndromes.

In April 2015, a task force of cardiac specialists from 17 biomedical institutions from around the world met in Shanghai, China, with the goal of developing both a clinical consensus report and a textbook to help the health care community better understand the mechanisms leading to J wave syndromes and to assist with diagnosing and treating the disorders.

The task force effort was led by Dr. Antzelevitch, professor and executive director of cardiovascular research at LIMR and director of research at Lankenau Heart Institute, and Dr. Yan, professor at LIMR and clinical cardiologist at Lankenau Medical Center.

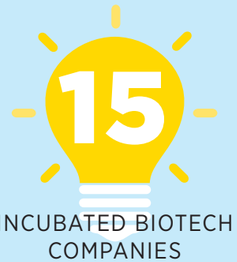


Months of work culminated this past summer in the publication of a textbook, *J Wave Syndromes: Brugada and Early Repolarization Syndromes*, and an expert consensus conference report published simultaneously in the medical journals *Heart Rhythm*, *Journal of Arrhythmia*, and *EP-Europace*.

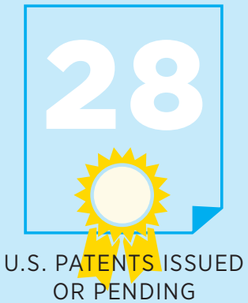
Of note, Drs. Antzelevitch and Yan discovered the cellular basis for the electrocardiographic J wave in 1996, and they were the first to link J waves to the syndrome of right bundle branch block, ST-segment elevation, and sudden death, which they named "Brugada syndrome" after the two Brugada brothers who first described this triad of clinical findings. Dr. Yan was the first to name "J wave syndromes" in the medical literature.

LIMR BY THE NUMBERS*

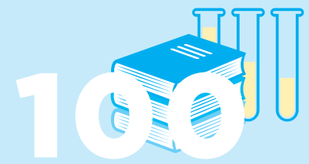
LIMR FACULTY INVENTIONS IN CLINICAL USE
(5 DRUGS, 4 TESTS)



INCUBATED BIOTECH COMPANIES



U.S. PATENTS ISSUED OR PENDING



TRAINEES
(GRADUATE, PhD, POSTDOC, MD)

*TOTALS SHOWN ARE FROM 1999 TO PRESENT

Illa G. Brustman

A Quiet Supporter's Lasting Legacy

Illa G. Brustman made an extraordinary gift to Lankenau Medical Center that she knew would come as a pleasant surprise.

Mrs. Brustman, a Narberth resident and corporate librarian for General Electric, was a grateful patient who contributed modest donations to Lankenau over the years. Upon her passing in 2009, Lankenau Medical Center Foundation learned that Mrs. Brustman had left a bequest and the residue of her estate to Lankenau, to the sum of more than $1 million.

Mrs. Brustman indicated that her gift should support research, an integral part of Lankenau's mission as a medical center. In keeping with this wish, her donation has gone on to benefit patients worldwide through support of investigative scientific work within the Preclinical Research Facility at Lankenau Institute for Medical Research (LIMR).

The Preclinical Research Facility is a state-of-the-art laboratory complex that allows LIMR scientists to perform crucial early investigations involved in discovery and development of new drugs, medical tests, and medical devices. It also enables major research funded by the National Institutes of Health and other federal agencies.

As this issue of *Catalyst* highlights, the Preclinical Research Facility plays a central role in LIMR's work, for example making possible:

- Development and testing of drugs to stimulate new tissue or organ regeneration after injury or loss
- Development and testing of a novel precision medicine approach to treatment of aggressive cancers
- Discoveries about how autoimmune diseases develop, as well as investigations of experimental medicines to reduce autoimmune damage

The late Rita Katten, a longtime friend of Mrs. Brustman and a steadfast Lankenau volunteer, described Mrs. Brustman as "the kind of friend everyone would want close by—generous and thoughtful, considerate and caring by inclination." As Ms. Katten added, "She didn't do things halfway."

Mrs. Brustman's gift was inspired by a love of mankind. She likely never considered the lasting legacy of her exceptional generosity, but the selflessness of her bequest captured the attention of the Lankenau Medical Center family and has gone on to benefit—and will continue to benefit—patients both near and far.

Main Line Health®

ABOUT MAIN LINE HEALTH

Main Line Health® is an integrated health system serving the Philadelphia region, with more than 2,000 physicians, one quaternary and three tertiary care hospitals, a wide network of patient care locations and community health centers, specialized facilities for rehabilitative medicine and drug and alcohol recovery, a home health service, and a biomedical research institute. Collectively, Main Line Health's physicians, care teams, health care facilities, and researchers provide patients with primary through highly specialized care as well as access to clinical trials.