LANKENAU INSTITUTE FOR MEDICAL RESEARCH

CATALYST

FALL 2019-WINTER 2020

LIMR’S NEXT GENERATION OF RESEARCHERS
Meet four young scientists who have devoted their careers to improving patient care via biomedical research | Page 3

ALSO:

Mission: Vanquish Sudden Cardiac Death
Page 2

Cardiac Research Today: Improving the Standard of Care for Tomorrow
Page 5

Your Investments in Research Can Have a Significant Impact
Page 8
IN THIS ISSUE

Beyond the Lab Walls: Caring for Our Community | 1
Mission: Vanquish Sudden Cardiac Death | 2
Cover Story: LIMR’s Next Generation of Researchers | 3
Cardiac Research Today: Improving the Standard of Care for Tomorrow | 5
LIMR News | 7
Your Investments in Research at LIMR Can Have a Significant Impact | 8

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, clinical 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.

Stay updated on LIMR news via social media

Facebook: fb.me/LankenauInstituteforMedicalResearch
Twitter: @LIMR_
LinkedIn: linkedin.com/company/limr
Periodically, LIMR researchers step away from the clinic or lab bench to engage with Main Line Health’s patient population and the broader community as a group, to discuss our discoveries and innovations, and to hear from others about their priorities in health and biomedical research. We believe these initiatives are crucial components of LIMR’s mission to advance human health and well-being.

Feedback from individuals in our community raise the attention of our researchers to issues about which we may not be aware or may not be prioritizing sufficiently. For example, in responding to cancer survivors, LIMR scientists recently developed a blood test that can predict which cancer patients will suffer from the most debilitating nausea after chemotherapy, something that clinicians saw (and could not manage well) but that the vast majority of lab researchers simply did not know much about.

Below are just a few more examples of our community outreach — both in-person and online — this past year. Such events help researchers learn where important but unseen opportunities for their work may exist.

In October, we hosted our second annual Population Health Day in which about 60 clinicians, patients and community members met to define and discuss important areas for research and collaboration in order to address patients’ health care needs. This community-wide conversation offered enlightening perspectives on barriers to health care equity; strategies for research that can lead to the best patient outcomes; and ways to eliminate disparities in health and wellness. The event, organized by the Main Line Health Center for Population Health Research at LIMR, was a rousing success, and we already are looking forward to Population Health Day 2020 in which our theme will be bioethics.

This past summer, we welcomed representatives from the regional office of the U.S. Health and Human Services (HHS) agency. Matt Baker, regional director of HHS, and Tom Harris, regional outreach specialist for HHS, visited Lankenau and LIMR to meet with executives and staff to discuss the contributions health systems like ours can make in researching and defining overall community health needs. We look forward to continuing engagement with HHS regional officials.

LIMR also is harnessing the far-reaching impact that social media can have in relaying important information to consumers. For example, this past summer two LIMR clinical trial professionals, Ann Marie Chikowski, division manager for cardiovascular research, and Michael Crown, senior clinical research coordinator, gave a terrific talk on the digital channel Facebook Live. Their topic: “Is a clinical trial right for you?” They discussed trial safety, eligibility criteria, the types of clinical studies available at Main Line Health and much more. Their talk garnered more than 1,400 Facebook views and, importantly, helped answer questions from patients and caregivers around the world about clinical trial participation.

Additionally, LIMR scientists this year wrote a series of consumer-focused articles called “Ask a Researcher,” in which they highlighted healthy-living tips based on biomedical research. Topics included cancer-reduction strategies from oncology researchers and heart care advice from cardiovascular researchers. The articles were distributed online to a wide variety of consumers and patients by our communications partners at Main Line Health. To read the articles, visit limr.org.

In short, we recognize that our responsibilities extend beyond our labs’ walls. These and our other outreach endeavors provide us with a valuable opportunity — no, a privilege — to help further advance the well-being of Main Line Health’s patient population and our broader community.

George C. Prendergast, PhD
The Havens Chair for Biomedical Research
President and CEO
Lankenau Institute for Medical Research, Main Line Health

BEYOND THE LAB WALLS: CARING FOR OUR COMMUNITY
Each year in the United States about 450,000 people succumb to sudden cardiac death (SCD), which is unexpected death from either a known or unknown preexisting cardiovascular condition. Even more distressing is that some victims are young, athletic and in the prime of their lives.

Determining the underlying causes of SCD is the life’s work of Gan-Xin Yan, MD, PhD, a world-renowned scientist-physician who splits his time between his research lab at LIMR and his practice as a cardiologist and electrophysiologist at Lankenau Heart Institute. In his practice he treats patients with arrhythmias (irregular heartbeats), atrial fibrillation and other cardiac disorders.

Patient Jean Marie Didominic of Ardmore, Pa., can’t say enough about Dr. Yan. “He is personable, caring and very knowledgeable,” she said. “He engaged me in my care. Sometimes he would come back later to say he’d been thinking about my care and had another idea. He goes out of his way to help patients.”

Over the years, his discoveries — made in the lab and the clinic — have contributed greatly to a better understanding of several syndromes and genetic abnormalities that can lead to SCD. For instance, he was part of a team, along with LIMR Professor Charles Antzelevitch, PhD, that discovered the cellular mechanisms underlying Brugada syndrome, a genetic disorder characterized by abnormal electrical activity within the heart that can lead to SCD. In 2004, Dr. Yan proposed the term J-wave syndromes, now widely used by clinicians, to encompass conditions such as Brugada syndrome and early repolarization syndrome as SCD-causing disorders.

But it’s his work as an innovator that has truly distinguished him from his colleagues.

**Wedge prep**

In the 1990s, Dr. Yan set out to devise a better method to determine cardiac electrochemical signals. At the time, scientists could record only the signals sensed on the outside of the heart muscle. “We didn’t know exactly what was happening inside of the heart,” recalled Dr. Yan.

While working as a junior faculty member in Dr. Antzelevitch’s lab, Dr. Yan developed a research method, called the arterially perfused ventricular wedge preparation (wedge prep for short), that can more accurately record all electrical signals in the heart, even in its innermost layers.

“Over the ensuing years, Dr. Yan demonstrated the wedge prep’s utility in determining the mechanisms underlying the development of life-threatening arrhythmias associated with many inherited syndromes, as well as in identifying drugs that can induce malignant arrhythmias associated with SCD,” said Dr. Antzelevitch. “It is a remarkable innovation.”

You can contribute to cardiac research at LIMR via the Cardiovascular Breakthrough Fund. For more, see page 8.
LIMR’s Next Generation of Researchers

Science, like most worthwhile pursuits, relies on great enthusiasm, energy and drive to maintain progress. At LIMR, these critical qualities are reinforced by bright young scientists who have devoted their careers to improving patient care via biomedical research. We thought you might enjoy meeting four of them.

Eric Alexander, PhD
Cancer researcher

In his role as research assistant professor in the lab of LIMR Deputy Director Susan Gilmour, PhD, Dr. Alexander is studying the effects of polyamines on tumors. Polyamines are small molecules that are greatly increased in tumors compared to normal tissues. The team members are not just studying polyamines’ mechanism of action, they also are developing agents that in preclinical studies show the ability to thwart that activity and stop cancer in its tracks.

“Our polyamine blockade therapy provides a dual attack on tumors by starving them of polyamine growth factors and by activating a specific immune attack on tumors,” said Dr. Alexander. “We’re very excited about the possibilities of this therapeutic approach.”

Their polyamine research has been funded by the National Cancer Institute, U.S. Department of Defense, Sharpe-Strumia Research Foundation, and John B. Deaver Auxiliary of the Women’s Board of Lankenau Medical Center.

Another promising project involves blocking the actions of thrombin, an enzyme in blood plasma that causes blood clots. Cancer patients are at increased risk for developing blood clots, a risk exacerbated by chemotherapy. Meanwhile, thrombin also stimulates cancer progression independent of clotting, making thrombin an attractive target for therapy. By adding thrombin blockade to frontline cancer treatments, LIMR scientists were able to significantly decrease the number of activated platelets and platelet-derived microparticles in the blood, while also reducing tumor growth and metastasis in preclinical studies of metastatic breast and ovarian cancers.

“Most cancers are associated with thrombic events, and in fact, such events are one of the leading causes of death in cancer patients,” said Dr. Alexander. “We’re testing oral anticoagulants to treat thrombic events that, in turn, could have beneficial effects for cancer patients.”

Dr. Alexander received his doctorate in molecular genetics from Wake Forest University, followed by a fellowship at Children’s Hospital of Philadelphia (CHOP). He and his wife, a pediatrician at CHOP, have two children. In his off hours he likes to read, mostly science fiction and ancient Greek history. Hiking and biking keep him fit.

Asked the most challenging part of his work, Dr. Alexander said, “In research much of what we try doesn’t work. But that’s instructive, too. I’m a glass-half-full kind of person, which comes in handy in this line of work.”

The future of research: (seated) Lauren Merlo, PhD, and Kyle McGregor, PhD; (standing) Eric Alexander, PhD, and Marie Webster, PhD.
Kyle McGregor, PhD
Population health researcher

An expert in research methodology, Dr. McGregor focuses much of his efforts on the ethical use of data as it relates to highly vulnerable patient populations.

“When I was an undergraduate, I saw people using statistics that they seemed to cherry-pick for their own purposes,” he recalled. “But I also saw that data could be used to tell stories about people’s lives. I started focusing on how we could get and use information that would pay respect to those whose data were represented, while gaining insights that could help them have healthier and better lives.”

Before being appointed assistant professor at the Main Line Health Center for Population Health Research at LIMR this past summer, Dr. McGregor served as director of pediatric mental health ethics at NYU Langone Health, New York City, where he was an assistant professor of child and adolescent psychiatry and population health.

He completed his doctorate on a National Center for Advancing Translational Sciences Award at Indiana University. During his training he also completed a fellowship in clinical ethics. He then completed two postdoctoral fellowships: the first as a National Library of Medicine fellow in medical informatics at Yale University, and the second at Columbia University.

At LIMR, his broad-ranging interests include empirical research ethics, data analytics and population health. “They all go together,” he explained. “How do we tell stories in health care? Answering that question propelled me into bioethics. For example, people are concerned about the ethical use of technology and data analytics. Unpacking that gray area between data and human stories is the challenge that drives me.”

He seeks to help Main Line Health appropriately respond to vulnerable patient populations, to ensure they have effective and cost-efficient care. “We have a responsibility to provide care to all, and all patients should be engaged in their own care. When they’re not, we need to ask why and how can we make it so?” He said this is especially important for a medical center like Lankenau that serves a diverse patient population.

In his spare time, Dr. McGregor enjoys international travel. His favorite destinations so far: Scotland, Dominican Republic and Prague. “My wife and I also love the fantastic restaurants in Philadelphia.”

Lauren Merlo, PhD
Autoimmune disease researcher

When the immune system goes awry, it can produce autoantibodies that attack the body, leading to autoimmune diseases such as rheumatoid arthritis (RA) and lupus. Unfortunately, there are no cures, only treatments to alleviate symptoms, and those treatments can have severe side effects. Discerning the underlying mechanisms that lead to autoimmune disorders would be a game-changer in medicine.

Dr. Merlo works every day with that goal in mind. In her role as research assistant professor in the lab of Associate Professor Laura Mandik-Nayak, PhD, Dr. Merlo studies IDO2, an enzyme discovered at LIMR that mediates the initiation and maintenance of inflammatory disease in preclinical studies of autoimmunity.

“We’ve found that IDO2 is a pro-inflammatory modulator of autoimmunity,” explained Dr. Merlo. “It acts in one component of the immune system: B cells. I’m interested in how IDO2 may affect the crosstalk between those B cells and other components of the immune system, thus impacting immunity as a whole.”

The team seeks to use its findings about IDO2 to develop a therapeutic approach for autoimmune diseases, particularly RA and lupus. “Imagine how incredible that would be if we could cure those conditions by targeting underlying causes,” said Dr. Merlo. The Women’s Board of Lankenau Medical Center agrees, and in 2019 it supported Dr. Merlo’s studies of IDO2 and its role in lupus.

Dr. Merlo started her science career in ecology and evolutionary biology, earning her doctorate in molecular evolution from the University of Minnesota. She then headed to the Wistar Institute, Philadelphia, for postdoctoral training in evolution and cancer biology. “I studied cancer biology as an ecological and evolutionary process,” she said. “There’s an ecology of cells, including immune cells, that interact with one another. That led to my interest in immunology and the immune cell populations underlying autoimmune diseases.”

In 2011 she came to LIMR to work in Dr. Mandik-Nayak’s lab. “At LIMR we have so many IDO pathway tools on which to test our theories,” she said. “We’re uniquely positioned in that regard, better than many other research institutes.”

In her down time, Dr. Merlo likes to read, take ballet classes and spend time with family. And her first love, ecology, has not abated. On any given weekend you’ll find her enjoying nature as she hikes in one of the parks in the tri-state area.
Marie Webster, PhD  
*Cancer researcher*

While melanoma accounts for less than 1 percent of all skin cancer cases, it causes most skin cancer deaths. LIMR Assistant Professor Dr. Marie Webster seeks to understand the cellular mechanisms that lead to disease progression and treatment resistance in melanoma.

Her path to this research interest began during her graduate work at Johns Hopkins School of Medicine where she synthesized and tested substances designed to activate and release a drug in the hypoxic environment of tumors. “When we tested our compound against a panel of cancer cell lines, we found that it had specificity toward melanoma,” she said.

That work piqued her interest in melanoma research, and she pursued it further at the Wistar Institute, first as a postdoctoral fellow, then as a staff scientist. Appointed to the resident faculty at LIMR this past summer, Dr. Webster seeks to determine how cancer cells change their character to gain the ability to metastasize and resist therapies. Specifically, she is studying changes in the Wnt signaling pathway, which regulates crucial aspects of cell function.

“Those changes occur during melanoma progression, but multiple types of stress, including aging, DNA damage and targeted therapy, also can promote changes in Wnt signaling. That, in turn, leads to the survival of a highly resistant subpopulation of cancer cells,” she noted. Her goal is to develop therapeutic strategies to target and kill these cancer cells.

Dr. Webster found her way to science at a young age. “As a child I wanted to be a medical doctor, but I also loved solving puzzles.” As she learned about the history of medicine, she realized she was more interested in research. “I love coming to work each day with the prospect of learning something new, perhaps something no one else yet knows,” she said. “I enjoy problem-solving and working through questions. Every day I work toward the goal of generating new therapies for patients with metastatic melanoma.”

In her spare time, Dr. Webster likes reading (mostly mysteries), running (oftentimes after her 3-year-old), and exploring area parks and museums.

In advancing her important work, Dr. Webster was awarded a prestigious career development award from the National Cancer Institute, the next phase of which is being pursued through her LIMR appointment. 🌟
Q: In what ways does clinical research advance patient care at Main Line Health?

Gray: At Main Line Health’s Lankenau Heart Institute, we have many of the best physicians in the region and, with the addition of the Heart Pavilion at Lankenau Medical Center, a spectacular environment for our patients to receive their treatment. Clinical research further adds to this excellence by providing us the ability to offer our patients the absolute latest and most advanced treatment options available.

Some of these modalities are important incremental improvements on existing treatments, and some represent revolutionary and transformational alternatives to cardiac conditions that heretofore were limited or had no options for relieving our patients’ symptoms. Ultimately, our research provides powerful tools to our practitioners to extend their mission of treating heart disease.

Q: You’ve been instrumental in bringing the Food and Drug Administration’s Early Feasibility Studies to Lankenau Heart Institute. What are those and why is it important to bring those trials to Lankenau?

Gray: An inconvenient truth regarding the timeline for medical device approval in the United States — and therefore patient access — became apparent several years ago to all involved; specifically, the average time to device approval lagged behind Europe and other developed countries by three to four years, but without a demonstrable benefit in terms of safety. To its credit, the FDA took a hard look at the reasons for this delay, some, but not all of which were hardwired into the way the approval process was structured. One of the most widespread realizations was that the process seemed to actually discourage early human research in the United States, while much of that necessary work was actually happening in other countries. This led to further concerns that, absent the FDA’s oversight in those other locations, there was uneven data-reporting quality and sometimes questionable patient protection.

So the FDA established several pathways meant to encourage earlier medical device human testing and promote device innovation inside the United States, all of which was intended to speed the approval process and, ultimately, patient access to new technology.

One of the primary programs in this regard is the Early Feasibility Study (EFS) pathway. It allows for first-in-human research to be performed in the United States with FDA oversight. To meet timelines these studies have specific aspirational metrics, such as time to contract approval in 60 days and first patient enrolled in another 60 days. To achieve this rapid trial initiation, 15 or so select U.S. institutions were invited to participate along with industry sponsors to develop a standard template for contracts that could be used broadly, so that each institution was not laboriously reinventing its own wheel.

Q: How have Main Line Health and LIMR been involved?

Gray: We have been involved, by invitation, from the very beginning of the EFS program. It’s because of the exceptional care Main Line Health provides, our physicians’ ability to recruit patients into research studies, and the excellent work our LIMR coordinators do in providing the most complete and accurate data on our research subjects — all of which constitute the cornerstones of quality clinical research.

Our participation in the EFS program over the past two years means we can provide Lankenau Heart Institute patients opportunities for care that are available in only a handful of advanced institutions in the world, truly the most up-to-date approaches typically not found anywhere in our region. It has also raised our game internally, and our LIMR coordinators are now managing some of the most complex protocols involving some of the most complex patient conditions — and doing it all without missing a beat.

Importantly, Main Line Health’s Lankenau Heart Institute has quickly become a known and respected site for this type of work, which has potentially far-reaching ramifications, including in the quality and number of fellowship applicants, invitations for future research, speaking engagements, etc. All of this is due to the remarkable efforts of many dedicated and talented people in the Lankenau Heart Institute and LIMR community.

Q: Switching gears, tell us about yourself. How do you like to spend your free time?

Gray: Well, I don’t get much spare time, but when I do, I like to spend it with my family. I also enjoy motorcycling to work, golfing, archery/bowhunting in season, and cycling.

You can contribute to cardiac research at LIMR via the Cardiovascular Breakthrough Fund. For more, see page 8.
LIMR investigator awarded DoD grant for studies on regenerating nerves, tissue lost from amputation

In a prior edition of Catalyst, we highlighted the groundbreaking work of LIMR Professor Ellen Heber-Katz, PhD, world renowned for her studies in regenerative medicine. We’re pleased to report that Dr. Heber-Katz and two colleagues were awarded a grant from the U.S. Department of Defense (DoD) for their further studies on a medication they developed that shows promise in regenerating nerves and tissue lost from amputation.

Dr. Heber-Katz made the surprising discovery in 1996 that a certain breed of laboratory mice can spontaneously regenerate lost tissue, similar to amphibians. Previously, it was thought mammals had lost the ability to regenerate tissue. The mice don’t just heal, Dr. Heber-Katz discovered. Rather, their injured tissue regenerates a perfect replica of lost tissue, including hair follicles and cartilage, without scarring and with total replacement of normal tissue and function.

Since that discovery, Dr. Heber-Katz pursued clues and determined that a protein, HIF-1a, is the likely cause of the tissue regeneration, which led the team to create a drug that mimics the protein’s action. “This DoD grant will help us progress our scientific understanding of HIF-1a and enable us to work on advancing future treatments that could eventually regenerate entire limbs,” said Dr. Heber-Katz.

DoD awarded LIMR $1.58 million, which will cover 88 percent of the project’s estimated cost. Non-governmental sources will fund $213,000, or 12 percent, of the project.
Your Investments in Research at LIMR Can Have a Significant Impact

You can designate one of the Lankenau Institute for Medical Research’s special funds to help precisely target your contributions to health care research that matters 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, enabling her and her team to continue groundbreaking work on this approach that holds enormous promise for the future of health care.

**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 after-effects 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.

**LIMR Unrestricted Fund**

Unrestricted gifts to LIMR are important in enabling opportunities to target your gift where our doctors and scientists believe it can have the greatest impact.

To donate to LIMR, please use the reply envelope inserted in this publication. You also can donate online at limr.org, and click on Supporters. Or call Rebekah Sassi, executive director of the Lankenau Medical Center Foundation, at 484.476.8067 or email sassir@mlhs.org.
THE POWER OF GIVING

Charitable giving does not require great wealth, only generosity of spirit and a desire to share what one has for the benefit of others.

A gift to Main Line Health’s Lankenau Institute for Medical Research (LIMR) has the potential to do great good. LIMR’s ultimate mission is to prevent disease and reduce suffering. Your support makes this possible.

To learn more, visit mainlinehealth.org/lmcgiving or call 484.476.8070.
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.