Main Line Health®

LANKENAU INSTITUTE FOR MEDICAL RESEARCH

CATALYST

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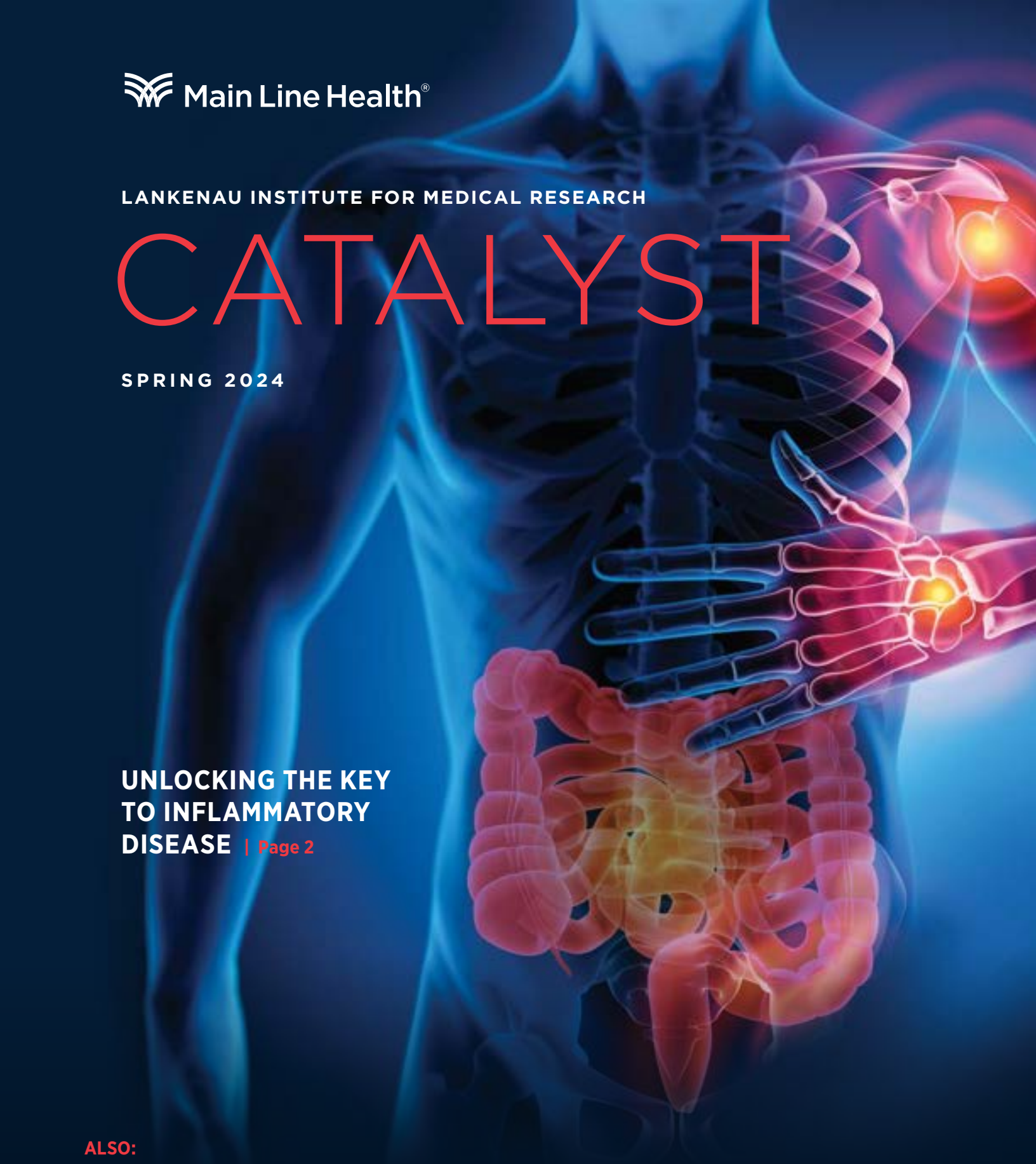

UNLOCKING THE KEY TO INFLAMMATORY DISEASE

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Lankenau Institute for Medical Research (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. Using its ACAPRENEURIAL™ model that integrates academic and entrepreneurial approaches, faculty and staff are devoted to advancing innovative new strategies to address formidable medical challenges including cancer, cardiovascular disease, tissue regeneration, gastrointestinal disorders and autoimmune diseases such as diabetes and arthritis. LIMR's principal investigators conduct basic, preclinical and clinical 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.

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George C. Prendergast, PhD

The Havens Chair for Biomedical Research

President and CEO

Lankenau Institute for Medical Research, Main Line Health

ACAPRENEURIAL™ approach leading LIMR toward cutting-edge treatments

This marks my 20th year at Lankenau Institute for Medical Research (LIMR), and it's impossible to overstate my admiration for the talented and dedicated group of scientists and clinician-scientists here who strive daily to expand the bounds of biomedical research. It is also incredibly rewarding to see how they have taken the ACAPRENEURIAL™ approach that I launched in 2004 — an academic/entrepreneurial hybrid that runs counter to nonprofit research norms by linking research pursuits to a culture of invention — and turned it into a dynamic reality. The tenets of this model are now being adopted elsewhere, including at Boston-based Arena BioWorks, and I believe many others will follow.

The efforts of our resident faculty have led to some of the most innovative, cutting-edge research with which I've ever been associated. One stellar example is the work of Patrick Viatour, PharmD, PhD, the subject of our cover story.

Dr. Viatour is a leader in studying cell division and its physiological impacts on the liver. His longstanding efforts with the liver have illuminated how the rapid cell proliferation common to chronic inflammatory diseases occurs. Dr. Viatour has leveraged this new knowledge by inventing a novel drug to control these diseases as a single class, with promising results in preclinical testing. From this foundation, he has received a federal grant to help him continue developing a drug that may widely be useful to treat arthritis, irritable bowel disease, Crohn's disease and many other immunologic disorders without the side effects of steroids, the current standard treatment.

This issue of *Catalyst* also covers the work of a radically new approach to treat metastatic cancers. This approach, which I have termed cryoimmune vaccination, is being pioneered by a company called Syncromune, with whom we are collaborating. Their methods build on new ways to use tumor cryotherapy, as studied in early-stage breast cancers by LIMR faculty members Margaretha Wallon, PhD; Ned Carp, MD; and Jennifer Sabol, MD; and Robin Ciocca, DO, of Main Line HealthCare.

Syncromune's approach applies the idea of freezing cancer cells at a single tumor site in individuals with metastatic cancer and then adds a second step — infusion of a multitargeted immunotherapeutic drug cocktail into the tumor. The initial step causes the tumor cells to fracture and release immune-stimulating neoantigens into the bloodstream, generating a personalized cancer vaccine in the patient. The second step — local infusion of four different immunotherapeutic drugs into the cryokilled tumor — bypasses the lethal toxicity that the same drug combination would produce if administered by intravenous infusion.

Strikingly, phase I trials of this combination treatment demonstrate responses in every tumor in the body, not just the injected site, with minimal side effects. LIMR has responded to this early data by setting up the first animal model for study to understand the treatment's systemic effects and how the new approach might best be leveraged in the clinic. Two pioneers at Syncromune developing this therapy, Charles J. Link, MD, who had previously moved LIMR's experimental class of oral immunotherapy drugs into clinical trials (IDO inhibitors), and Jonathan Lewis, MD, PhD, chief medical officer responsible for advancing clinical trials, have been appointed to our adjunct faculty to team up with LIMR on this potential breakthrough therapy.

I hope you find this edition as exciting and informative as I do.

Dr. Patrick Viatour, working with Drexel co-op research assistant Brenna Comeau, believes a treatment is on the horizon for chronic inflammatory diseases.

Unlocking the key to inflammatory disease

RESEARCH BY DR. PATRICK VIATOUR COULD LEAD TO TREATING ARTHRITIS, CROHN'S AND OTHER DISEASES WITH A SINGLE DRUG

In today's world of medicine, patients have become accustomed to seeking out the right specialist. Have arthritis? See a rheumatologist. Irritable bowel disease? A gastroenterologist. Cystic fibrosis involves various physicians — a pulmonologist for breathing issues, an endocrinologist for related diabetes and hormonal issues, and more.

But what if one medicine could treat many of those inflammatory diseases and others? Lankenau Institute for Medical Research (LIMR) researcher Patrick Viatour, PharmD, PhD, is optimistic that he is on a path where one drug, while not erasing the need for other specialists, could make their jobs easier and patients' lives better.

"Arthritis, irritable bowel disease, Crohn's disease and cystic fibrosis all have one thing in common," says the associate professor, who joined LIMR in 2021. "They are chronic inflammatory diseases. You may not think of it this way, but cancer is in that family of diseases, too, hijacking the immune system and causing inflammation to promote the disease's growth."

Dr. Viatour has made a believer out of the federal government. He has been awarded a grant from the high-risk, high-gain Innovative Science Accelerator Program, funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which supports hematological research.

In chronic inflammatory diseases, blood stem cells are stimulated to accelerate the production of inflammatory cells. Dr. Viatour has identified a dual mechanism that drives this cycle and now seeks to develop a drug to attack both arms of it, restoring appropriate blood cell production.

Steroids suppress the immune system and are currently the most effective way to treat chronic inflammation. But they carry a risk of side effects including weight gain, swelling, mood swings and insomnia. George Prendergast, PhD, President and CEO of LIMR, says Dr. Viatour's approach offers the promise of far less toxicity.

"This is extraordinary work that ties into what medical science learned during the battle against COVID-19," Dr. Prendergast says. "The innate immune system is like the front lines of an army, trying to limit infection and buying time until the adaptive immune system can learn a strategy to fight back more effectively. But COVID can trigger what's called a cytokine storm, sending the innate system into overdrive. The body would fight so hard that it was actually killing itself. Patrick's approach would regulate the innate system without steroids' side effects."

A nontraditional journey

Growing up in Belgium, Dr. Viatour wanted to be an astronaut. "I wanted to go where nobody had ever gone," he says. "Being from Belgium, that wasn't impossible, but pretty close. I realized my other love was research. So I switched from wanting to go to a place where nobody has ever gone to discovering something nobody has ever discovered."

He had no preference for what kind of research to pursue, but his postdoctoral mentor at Stanford University was studying the mechanism that regulates cell division in mice in relation to cancer.

"He was working with really advanced tools, and aberrant cell division is a hallmark of cancer," Dr. Viatour says. "This was it — something very important. From then on, all I wanted to do was use these kinds of tools to study cell division."

In particular, he grew fascinated with hematopoietic, or blood, stem cells. Every mature blood cell in the body — red blood cells, white blood cells and platelets — arises from these stem cells. Production begins early in the development of an embryo and continues throughout a person's life, occurring in organs and tissues including the bone marrow, spleen and liver.

Cancer and immunology tied together by one concept

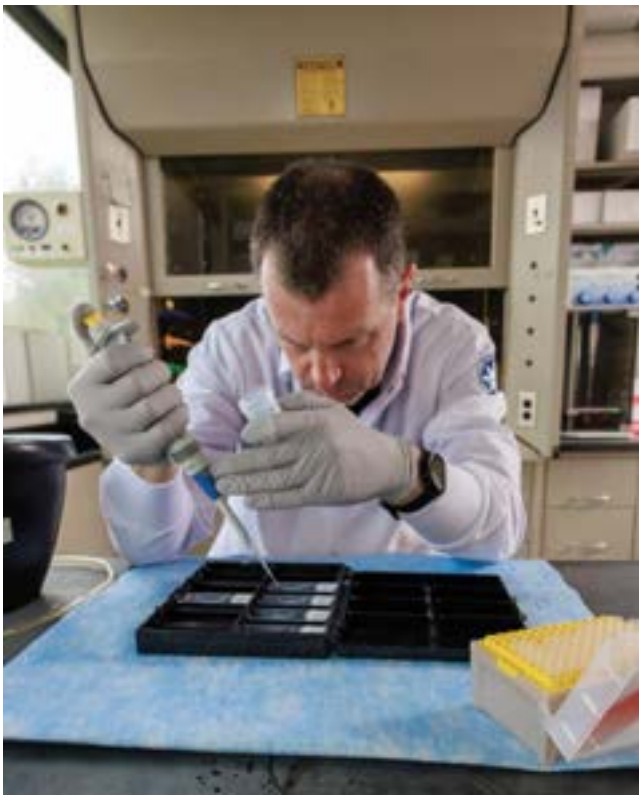
Dr. Viatour's research journey would take him places he never imagined. During his postdoctoral training and as an independent investigator, he has been working on two arms of research. One is cancer. The other is blood cell formation, which is part of immunology. He sees an important connection in these seemingly distinct studies.

"In both cases, even though the cancer type we study is a solid tumor and the blood cell formation is a liquid system, they operate by a similar concept," Dr. Viatour says. "They both involve abnormal cell division and rapid cell proliferation."

Although the NIDDK grant focuses only on inflammatory diseases, Dr. Viatour continues his cancer research on a parallel track and is optimistic that his current work will benefit liver cancer patients. He earlier received grant funding from the National Cancer Institute for it.

After 20 years, the mechanism is identified

Dr. Viatour spent 20 years searching for a mechanism that is common to all inflammatory diseases. Now, he says, he believes he's found it.



Dr. Patrick Viatour marks tissue sections with antibodies to detect protein expression.

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Biomedical research assistant Gabriella Oliva looks under the microscope at liver cells grown in three-dimensional culture conditions.

"My interest is not in how mature blood cells function during inflammation," he says. "I want to focus on the central mechanism guiding these cells' production by blood stem cells. I use the analogy that instead of destroying the tanks — in this case, mature blood cells — on the battlefield, I want to target the factory where the tanks are produced."

More specifically, inflammatory diseases produce cytokines. Those messengers alert the blood stem cells not only to increase the production of inflammatory cells but also to decrease the production of other blood cells, creating a dangerous imbalance.

Dr. Viatour has identified the two mechanisms that drive this imbalance and is developing a drug to inhibit both. He has made significant headway.

"In the lab, this drug has been able to restore blood production pretty much to normal levels," Dr. Viatour adds. "We still have a lot of work to do, but we're very excited by it."

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

INTERVIEW OF A LIFETIME — Deric Savior, MD, Co-Medical Director of Main Line Health Cancer Care and a Lankenau Institute for Medical Research (LIMR) faculty member, is shown during filming for The Balancing Act — a Lifetime television show hosted by Montel Williams and Olga Villaverde. He spoke about how to ensure diverse representation in trials for small cell lung cancer. Jessica Burrell, LIMR oncology clinical trials program manager, also was interviewed. The segment aired in March.

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

LIMR sponsoring its first-ever investigational device exemption trial

Dr. Ali Keramati

Dr. Steven Liskov

Lankenau Institute for Medical Research (LIMR) is sponsoring its first-ever investigational device exemption trial — a special Food and Drug Administration designation that paves the way for testing the safety and effectiveness of cutting-edge devices.

Ali Keramati, MD, a Main Line Health electrophysiologist and LIMR assistant professor, is the national principal investigator for the Left Bundle BRAVE study. Steven Liskov, MD, a LIMR research assistant professor, and Farah Olleik, MD, are subinvestigators.

Patients receive pacemakers capable of pacing in both the standard technique in the right ventricular area and the left bundle branch area to assess if the latter technique offers superior benefits. Standard pacing is associated with an uncommon but significant decline in heart function that may be preventable with the new technique, aimed at providing a more natural heartbeat.

Patients who have electrical conduction system disease after transcatheter aortic valve replacement undergo each pacing technique for nine months.

Company seeking to use AI to revolutionize drug design gains major backing

Dr. Mena Abdelsayed

OncoCardia, co-founded by Mena Abdelsayed, PhD, a research assistant professor at Lankenau Institute for Medical Research (LIMR), has secured a place within the prestigious NVIDIA Inception program with an advanced platform seeking to revolutionize drug design.

OncoCardia seeks to use AI and stem cell technology to reengineer failing drugs and enhance their safety and efficacy.

The elite NVIDIA Inception program comprises startups dedicated to driving transformative change across global industries, providing technological assistance and opportunities to connect with venture capital. OncoCardia is steered with the scientific guidance of George Prendergast, PhD, President and CEO of LIMR, and Mark Mercola, PhD, Dr. Abdelsayed's former postdoctoral supervisor at Stanford University. The company's other co-founder is Alice Yu, PhD, a Stanford alumna.

Dr. Abdelsayed has a track record in drug design. A drug known as AR-787, which he originally discovered and designed as a doctoral student at Simon Fraser University (SFU) to treat arrhythmias, was found by SFU and LIMR to have potential lifesaving results in the treatment of conditions leading to sudden cardiac death.

Dr. Karen Walsh and Dr. Katherine Chaves bolster LIMR faculty

Lankenau Institute for Medical Research (LIMR) has made additions to its faculty to strengthen its population health and gynecologic surgery research.

Dr. Karen Walsh

Dr. Katherine Chaves

Karen Walsh, DHSc, MS, MBA, PStat®, System Director for Performance Measurement, Improvement and Analytics at Main Line Health, has been appointed as a research assistant professor with the Main Line Health Center for Population Health Research at LIMR.

Dr. Walsh, a researcher and statistician, focuses on predictive modeling, clinical informatics and health services. Her most recent research is on multiple sclerosis (MS) and focuses on geographic variation in MS care, quality, value and predicting clinical endpoints.

Katherine Chaves, MS, MD, has been named a clinical assistant professor. Dr. Chaves is a board-certified OB/GYN with advanced training in minimally invasive gynecologic surgery. Her research interests include optimizing patient outcomes after gynecologic surgery, improving perioperative efficiency and ensuring equitable gynecologic surgical training.

Promising results from a novel treatment for metastatic cancer

IN AN EARLY TRIAL, A COMBINATION OF FREEZING PART OF A TUMOR AND INFUSING IMMUNOTHERAPY AGENTS RESULTS IN THE DESTRUCTION OF CANCER CELLS

Metastatic cancer is one of the grimmest terms in the English language, meaning tumor cells have migrated from the original site to other parts of the body. The greater the spread, the fewer the treatment options — and the lesser the chance of survival.

Results from an early trial by a company with ties to Lankenau Institute for Medical Research (LIMR) offer hope that a potent form of attack against this kind of disease is on the horizon.

A company called Syncromune has developed a novel combination therapy that involves freezing part of the tumor (cryolysis) and then conducting an infusion of four types of immunotherapy drugs. A phase I trial of the therapy, called SYNC-T, was conducted involving patients with metastatic castrate-resistant prostate cancer — prostate cancer that does not respond to hormone therapies.

Of 13 patients, 11 responded. In five of them, every tumor visible through imaging was gone. The other six had a partial response.

Results were so promising that the American Association for Cancer Research asked Charles J. Link, MD, a LIMR adjunct professor and co-founder and executive chairman of Syncromune, to present them at its annual meeting in April in San Diego. Jonathan Lewis, MD, Syncromune's chief medical officer and fellow LIMR adjunct professor, and George Prendergast, PhD, President and CEO of LIMR and a member of Syncromune's scientific advisory board, were among the presentation's co-authors.

The freezing of tumor cells essentially creates a personalized cancer vaccine that travels the body, Link says.

"It breaks open part of the cancer cells," he says. "That releases proteins that act like a vaccine. The process triggers activated T-cells to proliferate and circulate, destroying the cancer throughout the body."

Part of the impetus for pursuing cryoablation (treating a tumor at extreme cold temperature) came from work by LIMR faculty members Margaretha Wallon, PhD, Ned Carp, MD, and Jennifer Sabol, MD, and Robin Ciocca, DO, of Main Line HealthCare. Their work with cryoablation showed that, in rare cases, not only would destruction occur at the tumor site, but an immune response would result, too.

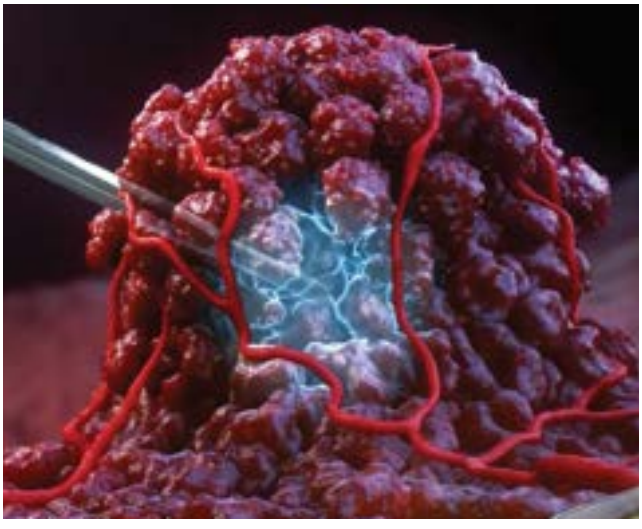
Trying combinations of immunotherapy agents to fight cancer is among the hottest areas of clinical research. However, administering large amounts of the drugs often results in not only intolerable but sometimes dangerous side effects.

Infusing the drugs directly into the tumor would allow them to be administered in smaller doses, reducing side effects while still getting powerful results, Dr. Link says. Upon settling on the approach, the job was to determine which of the available agents would be safe and effective in amplifying the cryotherapy's effects.

"Infusing the multitargeted immunotherapy at the right flow and rate immediately after freezing a portion of the tumor allows the proteins to drain from lymph nodes in a way that causes a very quick immune response," Dr. Lewis says.

Dr. Link has a long history with Dr. Prendergast. Dr. Link founded a company called NewLink Genetics Corp. that became LIMR's first spinoff company to go public. He said LIMR will be in the vanguard of Syncromune's development process going forward.

"There's no reason to think the majority of human cancers can't be approached with this method," Dr. Link says. "We are testing it in breast cancer already. This is the most exciting project I've ever been part of."



Representation of a small portion of a tumor being lysed (frozen) to expose neoantigens.

Cardiovascular trials contribute to comprehensive program to prevent stroke

More than five million people across the United States are estimated to have atrial fibrillation, the most common cardiac arrhythmia, which is caused by a disruption of the electrical signals that tell your heart when to pump blood. AFib occurs when the heart beats rapidly and irregularly, often described by patients as a flutter. The sensation is not one to ignore — those with the condition have an increased risk of stroke.

Lankenau Heart Institute has developed a comprehensive program focused on blood clots that form in a small pouch in the top left chamber of the heart called the left atrial appendage, where blood tends to pool in those with AFib. Ninety percent of blood clots — which can cause a stroke if they travel to the brain — form there.

"Most patients with atrial fibrillation can have their risk of stroke managed fairly easily by taking blood thinners to prevent clots," says Basel Ramlawi, MD, Chief of Cardiothoracic Surgery at Main Line Health, Co-Director of the Lankenau Heart Institute and a Lankenau Institute for Medical Research (LIMR) professor. "However, many people, particularly those who are older, can develop serious bleeding from these medications and require other options. We offer several procedures to close off the pouch and prevent clots from forming that have proven highly effective at stroke prevention."

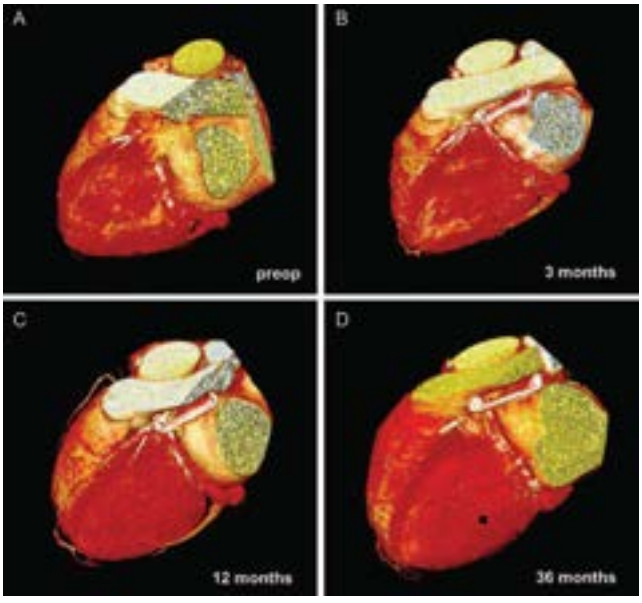
Leaders of the Lankenau Heart Institute are also top researchers at LIMR. That crossover has contributed to the development of a portfolio of minimally invasive options to close off the appendage.

At the heart of the program are the groundbreaking nonsurgically implanted Watchman FLX™ and Amplatzer™ Amulet™ devices. Main Line Health investigators' involvement in early clinical trials helped contribute to Food and Drug Administration approval of both devices, which reduce the risk of stroke without the bleeding concerns associated with long-term blood thinner use. Main Line Health continues to be at the forefront with the introduction of the novel Penditure™ device — a surgically implantable clip that comes preloaded on a single-use delivery system. Recently, Dr. Ramlawi successfully performed one of the nation's first deployments of the device.

Meanwhile, LIMR continues to conduct trials on the next generation of devices. The landmark Left Atrial Appendage Exclusion for Stroke Prevention (LeAAPS™) study seeks to establish a new standard of care through use of a device called AtriClip, which functions similarly to a bobby pin and is placed at the base of the pouch during cardiac surgery.

William Gray, MD, Chief of Cardiovascular Diseases at Main Line Health, Co-Director of the Lankenau Heart Institute and a LIMR and Thomas Jefferson University professor, was principal investigator of a first-in-human national trial for a device called the CLAAS® System and is the global co-principal investigator in the follow-up CONFORMAL trial. CLAAS is a unique second-generation device incorporating several improvements, including foam for a better seal. The study intends to compare it to Watchman and Amulet.

"Left atrial appendage closure is becoming an increasingly important alternative to anticoagulation for patients with atrial fibrillation," Dr. Gray says. "Although first-generation devices have been highly effective, there are significant limitations in some patients. I'm excited about the advances that we're making at Lankenau. We want to give patients the most effective, safest options to let them quickly resume living their lives."



A series of CT scan images of the heart before implanting the AtriClip device and then at three, 12 and 36 months afterward. (AtriClip visually resembles a clip and can be seen at the top center of panels B, C and D.) The scan shows complete closure of the left atrial appendage from outside the heart (and no contact with blood inside the heart), reducing the chance of stroke.

Gift boosts hope of reducing life-threatening diabetes complications

JERRY AND ANNETTE TIFFAN SEE LIMR'S RESEARCH INTO A KEY MOLECULE AS A PATH TO UNDERSTANDING THE CONNECTION BETWEEN DIABETES AND HEART RISK

Gerald (Jerry) L. Tiffan saw early professional success as a field manager working for Goodyear Tire & Rubber in the racing division at the Akron, Ohio, corporate home office. During that time, Jerry met Roger Penske, who asked him to join the Penske Corp., where he managed newly acquired operations in Michigan, New Jersey and Pennsylvania. After some time, he and his business partner acquired the Pennsylvania-based company, which had operations statewide, and expanded into upstate New York and California before he eventually sold it and retired.

In a sense, he and his wife, Annette, saw healthcare success also. "As a young couple in Pennsylvania," Annette says, "we had no health issues. All I ever needed was my OB/GYN, dentist and our annual physicals. That was our introduction to healthcare."

Good health continued into their later years, but everything changed in September 2019 when Jerry had a cardiac episode and was admitted to Lankenau Medical Center, part of Main Line Health. He required surgery, which was performed by cardiothoracic surgeon Francis Sutter, DO.

Both Jerry and Annette have been thrilled with the level of care at Lankenau Medical Center ever since, saying that even though it is a large teaching hospital, it has the feel of a community hospital where everyone knows you.

"They are all such professionals and genuinely care," says Annette, who had her own serious health scare — a tumor that was operated on at Bryn Mawr Hospital, also part of Main Line Health.

As a result of their experiences, when Jerry and Annette heard about the systemwide campaign to support cardiovascular research conducted by Lankenau Institute for Medical Research (LIMR), it struck a chord and they decided to give a substantial gift.

Specifically, they chose to support research into a potential treatment for life-threatening diabetes complications. The research team is studying the effects of a glucose-derived molecule called 3-deoxyglucosone (3DG) that has seen relatively little investigation to date. Innovative drugs that safely lower 3DG may hold the key to preventing these

complications, including heart attacks. In particular, Jerry is interested in 3DG because of his interest in advancing cardiovascular research.

Coupling the Tiffans' gift with a federal grant, LIMR scientists are seeking to identify new drug candidates that can block production of the disease-causing molecule.

"Supporting something that is closer to clinical trial is important because we may be able to have an impact sooner than later," Jerry says. "When we make a gift, it's important that it is put to good use."

Jerry is encouraged to know that their gift was nearly enough to fund the initiative's entire remaining need. Sometimes, he says, giving a gift can feel like it is making just a small dent in a large problem. But when they can see that their gift will move a drug into a clinical trial, they are enthused and hope to hear results from LIMR in the near future.

"We are usually private people, but we hope our story can encourage someone else to give," Jerry says. "Both of us would like others to experience the lifesaving care that we have. Whichever way we can do that, we're willing to help."

Your investments in research at LIMR can have a significant impact

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

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 our studies on targeted nano-carrier therapeutics as experimental treatments for cancer and our work on cloned human antibodies as treatments for infectious disease, cancer and neurological illnesses.

Cardiovascular Breakthrough Fund

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

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.

LIMR Unrestricted Fund

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

To make a donation, please use the reply envelope inserted in this publication, or donate online at limr.org (click on Giving). You may also call Katie Beddis of the Lankenau Medical Center Foundation at 484.476.8067, or email her at beddisk@mlhs.org.

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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.