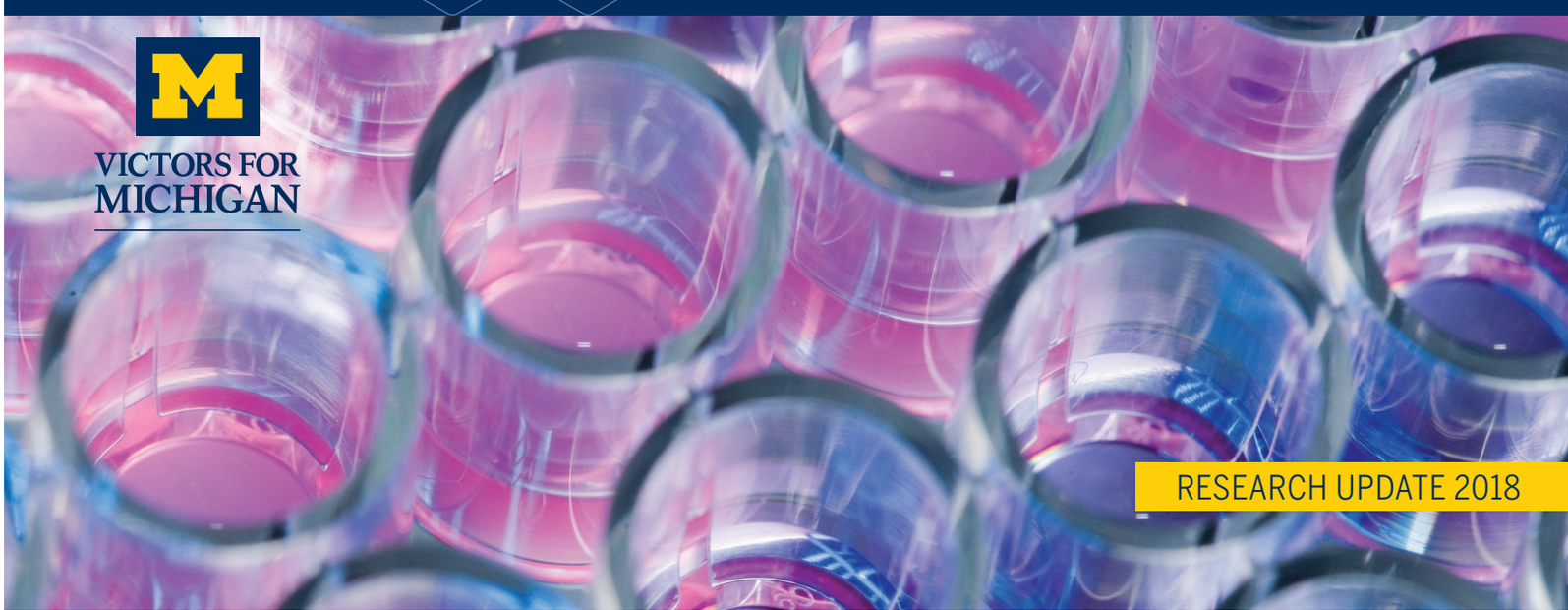
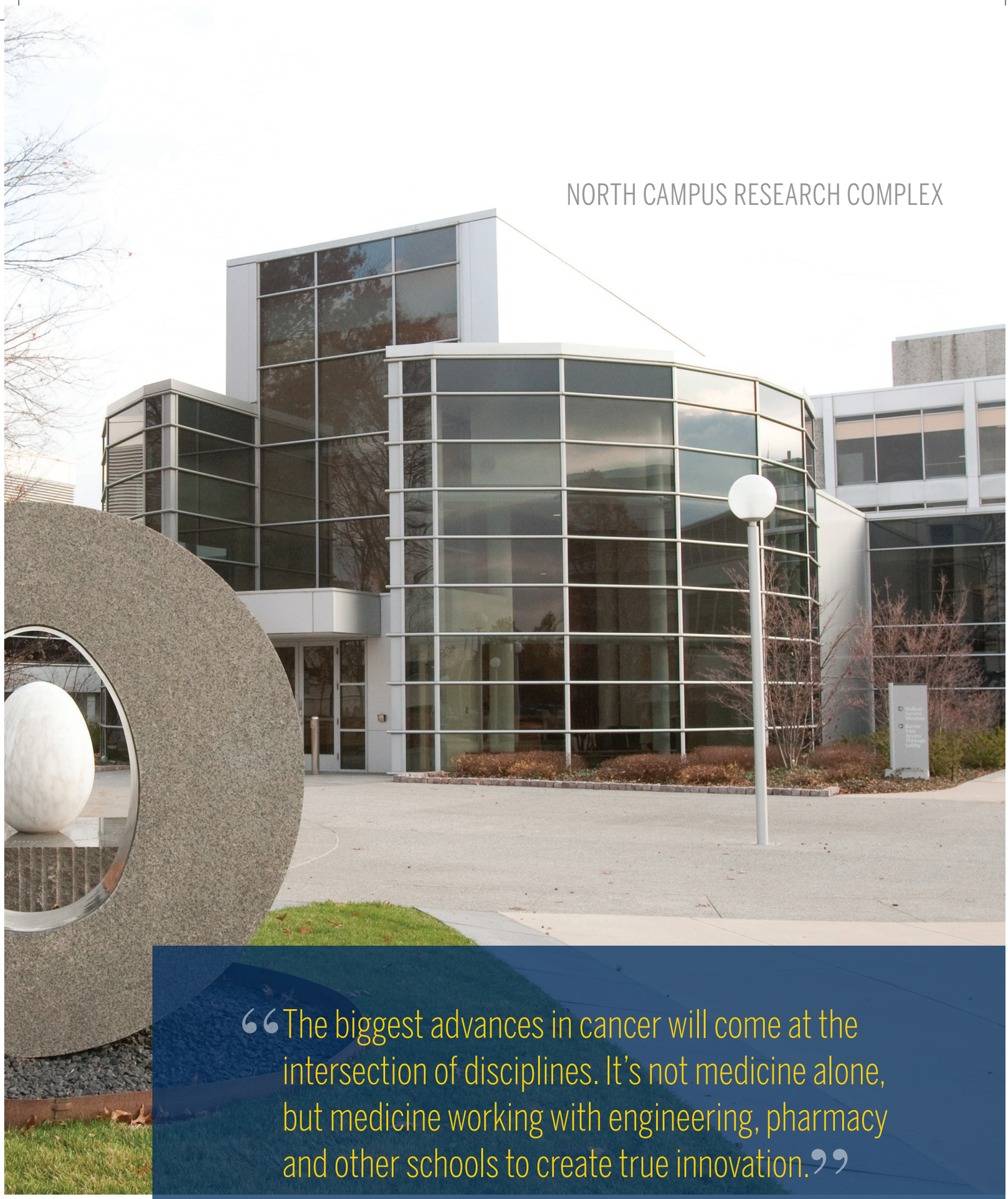
FORBES INSTITUTE FOR CANCER DISCOVERY
MICHIGAN MEDICINE

The end of cancer begins here.

VICTORS FOR MICHIGAN



RESEARCH UPDATE 2018



NORTH CAMPUS RESEARCH COMPLEX

“The biggest advances in cancer will come at the intersection of disciplines. It’s not medicine alone, but medicine working with engineering, pharmacy and other schools to create true innovation.”

— MAX S. WICHA, M.D.

ON OUR WAY

When we launched the Forbes Institute for Cancer Discovery at the University of Michigan Comprehensive Cancer Center in June 2016, our goal was to fuel game-changing initiatives that would drive breakthroughs in cancer research.

Today, it is a pleasure to report that our first grants — awarded in March of last year — have yielded exciting and promising results. Support was given to four senior Forbes scholars who have put together teams of scientists to pursue progress toward personalized immunotherapy, identifying a new drug for pancreatic cancer, targeting a complex gene that drives the growth of many cancerous tumors, and advancing an implantable device designed to attract migrating cancer cells within the body before they spread to other organs. The collective impact of these projects could transform the way we treat cancer.

We also leveraged the Director's Innovation Fund to support promising technology development projects as well as to purchase two leading-edge pieces of equipment that will enable faculty to pursue exciting new research studies.

In creating the institute, the Forbes family was wonderfully forward-thinking in its commitment to engaging researchers across disciplines. In the following pages, you'll learn more about the work of faculty from the Medical School, the Department of Biomedical Engineering (which is a partnership between the Medical School and the College of Engineering), the College of Pharmacy, the Department of Mathematics, and more. These faculty members are working together to improve and save the lives of those facing cancer.

As an institute we are just getting started, and we are grateful that you are part of the team. We appreciate your interest, your contributions, and your encouragement. I hope you will feel free to reach out to me if you have any questions about this or other cancer research.

With gratitude from the Forbes family, from me, and from all those whose work is being supported,

MAX S. WICHA, M.D.
Madeline and Sidney Forbes Professor of Oncology
Director, Forbes Institute for Cancer Discovery
Founding Director Emeritus, University of Michigan Comprehensive Cancer Center

GRANT TITLE

Toward Personalized Cancer Immunotherapy: An Opportunity to Accelerate Clinical Development

RESEARCHERS

Senior Forbes Scholar
James J. Moon, Ph.D.

Anna Schwendeman, Ph.D.

Improving the Odds for Success in Immunotherapy

Cancer immunotherapy has recently made international headlines with the striking clinical success of immune checkpoint inhibitors, which are drugs that enable the immune system, including immune system T cells, to better fight cancer. These therapies, however, currently work in only 10 percent to 30 percent of patients.

To improve those statistics and evoke effective and lasting immune responses, Drs. Moon and Schwendeman have developed a novel technology that can significantly boost the anti-tumor efficacy of immune checkpoint inhibitors, eliciting 31-fold greater frequencies of killer T cells.

In their approach, they assemble proteins into ultra-small nanodiscs that improve drug delivery to the immune system's lymphoid organs. This is referred to as a cancer vaccine because it triggers the patient's immune system to attack cancer cells.

With support from the Forbes Institute, the team demonstrated that nanodisc vaccination in combination with immune checkpoint inhibitors can eradicate large, difficult-to-treat melanoma tumors in 85 percent of laboratory models. Furthermore, the team showed that nanodisc vaccines work with human tumor neo-antigens derived from a melanoma patient.

Drs. Moon and Schwendeman have partnered with biotech executive William Brinkerhoff to form EVOQ Therapeutics, which will bring these exciting results from the laboratory to the clinic. Their goal: start a first-in-human clinical study within the next two years.

The team's nanodisc vaccine technology represents a new, powerful, convenient, and safe approach for personalized cancer immunotherapy. It has the potential to improve outcomes for cancer patients and transform the treatment of cancer.

JAMES J. MOON, PH.D., is the John Gideon Searle Assistant Professor of Pharmaceutical Sciences and an assistant professor of biomedical engineering. His research program is focused on developing engineering tools for improving vaccines and immunotherapies. He has received numerous awards, including a National Science Foundation CAREER Award, a Department of Defense Career Development Award, and a Melanoma Research Alliance Young Investigator Award.

ANNA SCHWENDEMAN, PH.D., is an assistant professor of pharmaceutical sciences. She spent 12 years in the pharmaceutical industry, including serving as vice president of preclinical development at ONL Therapeutics and in various roles at Cerenis Therapeutics, Pfizer, and Esperion Therapeutics. She was involved in discovery and translation of several HDL cholesterol therapies to phase II clinical trials.

Senior Forbes Scholar James J. Moon, Ph.D., and Anna Schwendeman, Ph.D., (foreground) update members of the U-M Comprehensive Cancer Center's National Advisory Board on their research progress.

GRANT TITLE

Discovery of Next-Generation Therapeutics Through Machine-Learning Techniques

RESEARCHERS

Senior Forbes Scholar
Nouri Neamati, Ph.D.

Mats Ljungman, Ph.D.

Duxin Sun, Ph.D.

Vaibhav Sahai, M.D.

Developing a New Drug for Pancreatic Cancer

There is an urgent need to create innovative technologies that will aid the discovery of highly effective drugs for hard-to-treat diseases such as pancreatic cancer. Current drugs used to treat pancreatic cancer are not effective, and about 86 percent of patients succumb to their disease in less than five years.

A critical step in drug discovery is matching potential biological targets with compounds that may be able to intervene to change the course of a disease. To do this as quickly and effectively as possible, Dr. Neamati and the grant team have built a database of over 10 million small-molecule compounds that is searchable in two- and three-dimensions, as well as a larger database of 2 billion structures comprising the top 200 conformations for each compound.

Using machine learning techniques coupled with intensive bioinformatics analysis, the team identified 50,000 compounds that have properties very similar to FDA-approved drugs but that have never been tested in animals or humans. They acquired 40,000 of these compounds and have screened 20,000 in phenotypic assays. They have successfully identified 600 molecules that are active in several cancer cell lines. Based on these lead compounds, they have designed a series of highly promising analogues for the treatment of several cancers.

Through high-level comparisons with standard-of-care drugs, the Forbes Institute grant enabled the team to investigate and develop an understanding of the mechanism of action of each compound, or how it would produce its pharmacological effect. They then performed next-generation sequencing analysis on 80 of their novel compounds in representative cancer cell lines. They did the same for 30 drugs currently used in treatment. Significantly, they discovered that some of the newly identified compounds show remarkable similarity in gene expression profiles with clinically used drugs. The new compounds belong to a different chemical class and should exhibit different biological, pharmaceutical, and safety profiles.

NOURI NEAMATI, PH.D., is the John G. Searle Professor of Medicinal Chemistry in the University of Michigan College of Pharmacy. He has been recognized by numerous awards, has published more than 200 peer-reviewed articles, and holds more than 30 patents in the area of drug design and discovery.

MATS LJUNGMAN, PH.D., is a professor of radiation oncology and environmental health sciences. His laboratory is part of the Cancer Center's Translational Oncology Program and is focused on studying gene expression in normal physiology, cancer and neurological diseases as well as the development of cancer therapies.

DUXIN SUN, PH.D., is a professor of pharmaceutical sciences and the J.G. Searle Endowed Professor of Pharmaceutical Sciences. He serves as the director of the pharmacokinetics core. Dr. Sun has published more than 150 papers and holds 12 patents. He has supervised 29 Ph.D. students and 40 postdoctoral fellows and visiting scientists.

During the grant period, the team has performed stability studies and determined the pharmacokinetic properties as well as potential metabolites of a potential lead compound. The compound shows favorable pharmacological properties warranting further investigation. Importantly, they designed and synthesized 10 additional compounds with similar activity profiles in pancreatic cancer cell lines. In parallel, they determined the gene expression profile of a representative pancreatic cancer cell line treated with 11 clinically used drugs. Currently, they are performing bioinformatics analyses to identify unique pathways altered by these drugs in order to uncover which one of these drugs correlates with the new compounds. Successful completion of these studies will lead to selection of a new drug candidate for future clinical investigations at the University of Michigan.

Thanks to the Forbes Institute, the team was able to expand the use of their turnkey technology to pursue the preclinical development of a very promising compound for the treatment of pancreatic cancer.

VAIBHAV SAHAI, M.D., is an assistant professor of internal medicine who specializes in medical oncology and hematology. His research focuses on experimental therapeutics in pancreatic and biliary tract cancer.

GRANT TITLE

Drugging the Undruggable: Design of Novel KRAS Inhibitors by Dual Targeting of the Effector and Allosteric Binding Sites

RESEARCHERS

Senior Forbes Scholar
Judy Leopold, Ph.D.

Carol Fierke, Ph.D.

Taking an Innovative New Approach to a Common Cancer Gene

An oncogene is a gene that has the potential to create cancer, and the KRAS oncogene is the most frequently mutated oncogene in human cancer. It is a protein that drives the progression of a large percentage of tumors, including those originating in the colon and pancreas. But KRAS has long been viewed as an undruggable biological target because of the complexities associated with directly interfering with its tumor-building activity.

The overall objective of this research project is to design, synthesize, and optimize the development of small molecule inhibitors of KRAS protein-protein interactions to treat KRAS mutant cancers. During the grant period, funding from the Forbes Institute enabled Drs. Leopold and Fierke to complete the design and synthesis of 16 chemically distinct molecules designed to bind to KRAS and impair its ability to promote tumor growth. All sixteen molecules have been tested for their potential to interfere with the ability of KRAS to become activated.

The team is encouraged by preliminary results showing that a subset of these compounds are candidates for further testing in pancreatic and colorectal tumor cells. Studies are ongoing to determine whether these interesting drug-like molecules are capable of selectively impeding growth of tumor cells compared to normal, non-malignant cells.

JUDY LEOPOLD, PH.D., is a research professor of radiology and pharmacy and co-director of the Experimental Therapeutics Program at the University of Michigan Comprehensive Cancer Center. Before joining the U-M in 2009, she was the executive director of the Mechanistic and Target Biology Department at Pfizer Global Research and Development in Ann Arbor. She has led multiple cross-disciplinary research teams in advancing clinical drug candidates.

CAROL FIERKE, PH.D., is provost and executive vice president at Texas A&M University. She formerly served as dean of the Rackham Graduate School and vice provost for academic affairs for graduate studies at U-M.

GRANT TITLE

A Synthetic Pre-Metastatic Niche for Early Metastasis Detection

RESEARCHERS

Senior Forbes Scholar
Lonnie D. Shea, Ph.D.

Jacqueline S. Jeruss, M.D., Ph.D.

Advancing an Implantable Device for Attracting Cancer Cells Before They Spread

When a cancer recurs or spreads, forming a secondary malignant growth, that is the point it may become untreatable — and eventually lethal. Metastatic disease typically progresses by the migration of cells from a primary tumor, which enter the circulation. These circulating tumor cells (CTCs) eventually home to and colonize a permissive environment within a solid organ.

The permissive environment is called a pre-metastatic niche. In previous studies, Drs. Shea and Jeruss developed a synthetic pre-metastatic niche designed to mimic the environment in organs that might attract cancer cells. Their implantable technology is a microporous polymer scaffold that attracts immune cells, and the immune cells draw in cancer cells. If the device was implanted in a patient whose cancer is at risk of spreading, it could attract immune cells and cancer cells before they head to the lungs, liver or brain.

The team has now expanded the scope of their project to identify additional uses for the scaffold. By identifying progressive differences in immune cell populations within the scaffold, they hypothesized that characterizing the molecular underpinnings of the immunological microenvironment in the scaffold could inform therapeutic interventions. To test this hypothesis, they analyzed the immune cell population dynamics within the scaffold during the early onset of metastatic disease.

They discovered that the attraction of metastatic cancer cells is mediated, in part, by the immune microenvironment of the pre-metastatic niche and the recruitment of tumor-associated myeloid-derived suppressor cells, a hallmark of many diverse types of cancers. They then investigated whether changes in cellular composition would result in significant gene expression changes that correlate with the stage of disease (healthy, pre-metastatic, early metastatic, and late metastatic). A gene signature was identified from the scaffold that corresponded with each stage of disease.

Their findings suggest that the scaffold can be employed as a cancer detection system. Furthermore, they studied whether the scaffold could be used to monitor a response to therapy with positive results. Respectively, these studies support the use of scaffolds as a system to monitor disease progression and response to therapy, and the team is in the process of seeking support for clinical studies.

LONNIE D. SHEA, PH.D., is the William and Valerie Hall Chair and professor of biomedical engineering, a position he has held since 2014. He previously served on the faculty at Northwestern University. He has published more than 150 manuscripts, and has numerous inventions to his credit.

JACQUELINE S. JERUSS, M.D., PH.D., is an associate professor of surgery, pathology and biomedical engineering, and is director of the Breast Care Center at U-M. She joined the faculty in 2014 after serving on the faculty at Northwestern University. She cares for patients and shares a U-M Translational Oncology Program laboratory with Dr. Shea, where they are developing novel therapies for aggressive breast cancer subtypes and finding new approaches to managing the spread of cancer.

“Defeating cancer will take victors to move the process along and continue the fight toward conquering this dreadful disease. There is no better place to lead this fight than the University of Michigan.”

— SIDNEY FORBES

Funding New Tools to Propel Cancer Research Forward

The Forbes Institute has established a Director's Innovation Fund that enables us to both support the development of and purchase cutting-edge technology. In our first uses of the fund, we provided grants to two individuals who are bringing engineering and mathematical expertise to cancer research by inventing new approaches to studying the disease. And we purchased two pieces of research equipment.

One award was granted to support the work of Yu-Chih Chen, Ph.D., a postdoctoral fellow in the laboratory of Euisik Yoon, Ph.D., professor of electrical engineering and computer science, a professor of biomedical engineering, and director of the Lurie Nanofabrication Facility. Dr. Chen is a leader in Dr. Yoon's laboratory group, which developed a microfluidic device that handles tiny amounts of liquid to sort cancer cells based on their motility or ability to move spontaneously. Dr. Chen is helping to advance the technology to enable cancer researchers to sort and study cancer cells that would be most likely to spread throughout the body, leading to metastatic disease. Specifically, he is focused on using the technology to capture single circulating tumor cells that can then be genetically sequenced to understand the nature of an individual's cancer — ultimately enabling personalized treatment selection and improved treatment monitoring for patients.

A second award was given in support of a project led by Indika Rajapakse, Ph.D., an assistant professor of computational medicine and bioinformatics, and an assistant professor of mathematics. Dr. Rajapakse's team is building a data-guided mathematical algorithm to inform direct reprogramming of any cell into any target cell. In a recent paper published in the *Proceedings of the National Academy of Sciences*, he lays out an efficient way to directly reprogram cells. The team's long-term goal is to develop strategies for direct reprogramming of normal and abnormal cells, including cancer stem cells.

The Forbes Institute also has invested in a Fluidigm C1, a device that enables scientists to isolate and study individual cells and their DNA, **and a mass spectrometry imaging system**, which generates images of the spatial distribution of peptides, lipids, metabolites and drug molecules. This system can be used to study cancer cell heterogeneity, tumor microenvironments, metabolism, biomarker identification, drug distribution on tissue sections, and more. Both will have a broad impact on our research.

CANCER NEEDS VICTORS

Join us! The Forbes Institute for Cancer Discovery was founded by Sidney and Madeline Forbes, longtime Detroit-area philanthropists and dedicated friends and supporters of the University of Michigan. Nathan Forbes represents the family's dedication to high-impact research on the U-M Comprehensive Cancer Center's National Advisory Board. The Forbes Institute's grants are solely funded by gifts from donors, and the Forbes family invites everyone inspired to advance cancer knowledge toward cures to be a partner in its mission.

For more information or to make a contribution, visit **mcancer.org/ForbesInstitute** or contact

Kimberly A. Morris
Director of Cancer Programs
Michigan Medicine Office of Development, University of Michigan
734-763-5052
kimorris@med.umich.edu