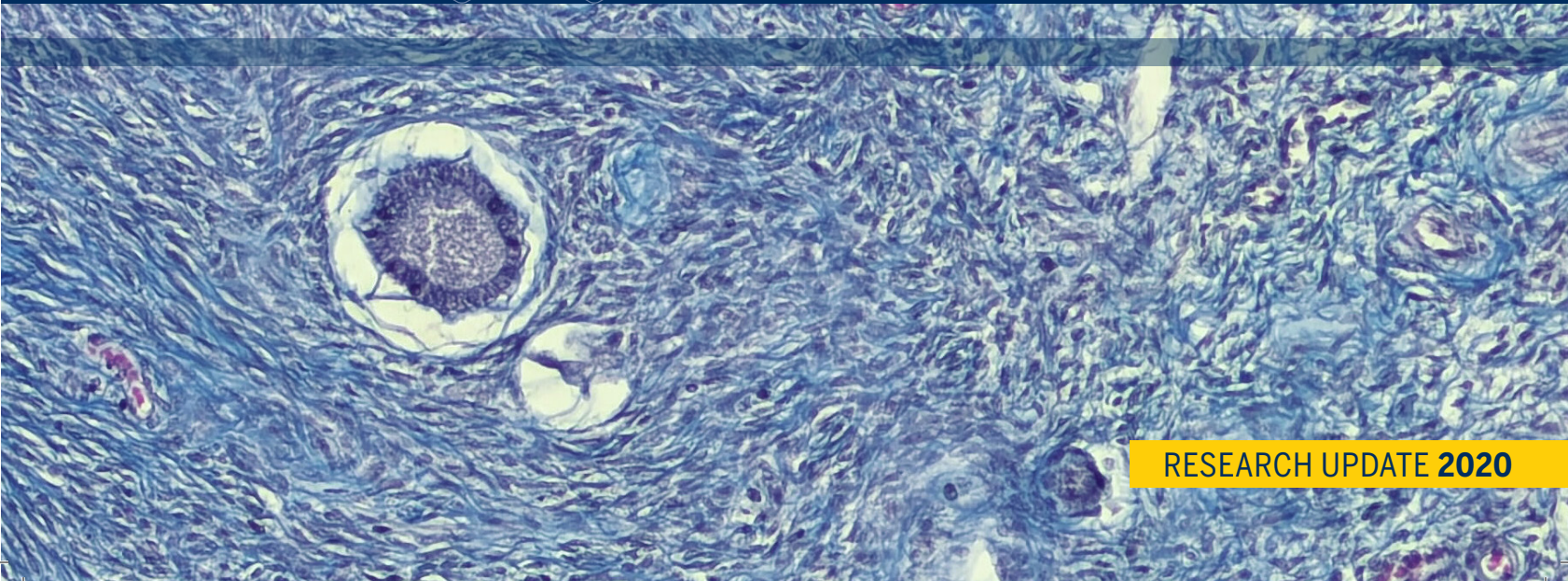




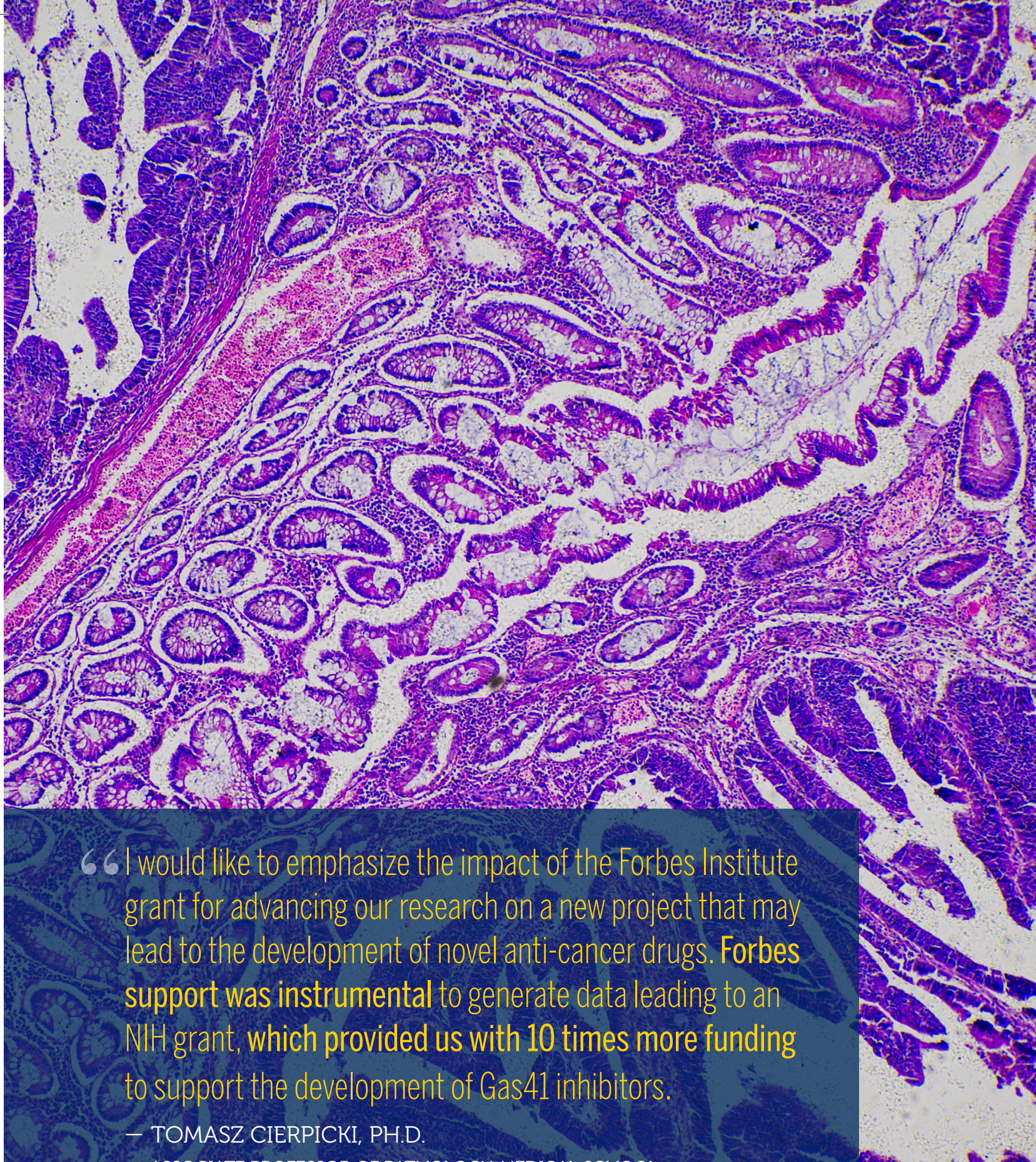
FORBES INSTITUTE FOR CANCER DISCOVERY  
MICHIGAN MEDICINE



# Advancing a New Era in Cancer Research



RESEARCH UPDATE 2020



“ I would like to emphasize the impact of the Forbes Institute grant for advancing our research on a new project that may lead to the development of novel anti-cancer drugs. **Forbes support was instrumental** to generate data leading to an NIH grant, **which provided us with 10 times more funding** to support the development of Gas41 inhibitors.

— TOMASZ CIERPICKI, PH.D.

ASSOCIATE PROFESSOR OF PATHOLOGY, MEDICAL SCHOOL

ASSOCIATE PROFESSOR OF BIOPHYSICS, COLLEGE OF LITERATURE, SCIENCE, AND THE ARTS

# MAINTAINING STRONG PROGRESS DURING A DIFFICULT YEAR

## DEAR FRIENDS:

2020 was a challenging year, but the University of Michigan adapted well to the COVID-19 crisis. Laboratory research continued to move forward despite the pandemic, with researchers coming into the labs in shifts so that everyone could stay safe.

The Forbes Institute for Cancer Discovery is now in its fifth year, and we have supported 34 investigators and 13 successful projects. Those named as awardees in 2019 pushed us in new directions in 2020, and they made strong progress toward lifesaving cancer treatments. We are pleased to share the results of their work as well as data that demonstrates the significant impact the Forbes Institute has had since its inception.

There have been major advances in cancer research over the last five years, especially in immunotherapy, genetics, and targeted therapies – some of the areas you will read about here. Patients are living longer, and living better, with fewer side effects.

We still have great challenges ahead, and many of the cancers that we are tackling at the Forbes Institute are particularly difficult, like brain, lung, and pancreatic cancers.

So not only is it an exciting time now, but it is really exciting as we move ahead. We look forward to continuing to keep you up-to-date.

With gratitude for your interest and support,

### MAX S. WICHA, M.D.

Madeline and Sidney Forbes Professor of Oncology  
Director, Forbes Institute for Cancer Discovery  
Founding Director Emeritus, University of Michigan Rogel Cancer Center



Forbes Scholars who received grants from 2017-19 report back on progress, promise:\*

59

Total number of grants

\$68.5 million

Outside grant funding received by Forbes Scholars

320

Total publications by Forbes Scholars

\$25 million+

Outside grant funding earned to advance research projects

12

Publications resulting from Forbes Institute research projects

30+

Invited talks and seminars, including keynote addresses, directly related to work completed in Forbes Institute projects

\*With all teams and 17 individual faculty members represented

# In Support of a Visionary Cancer Leader

The Madeline and Sidney Forbes Professor of Oncology



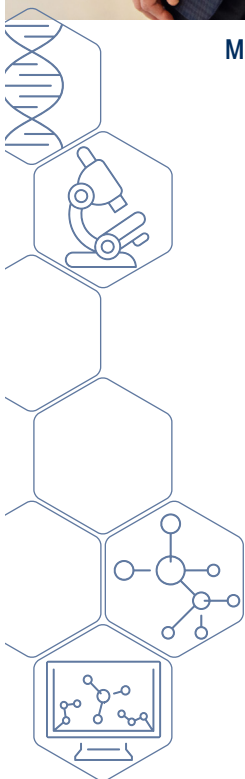
Max Wicha, M.D.

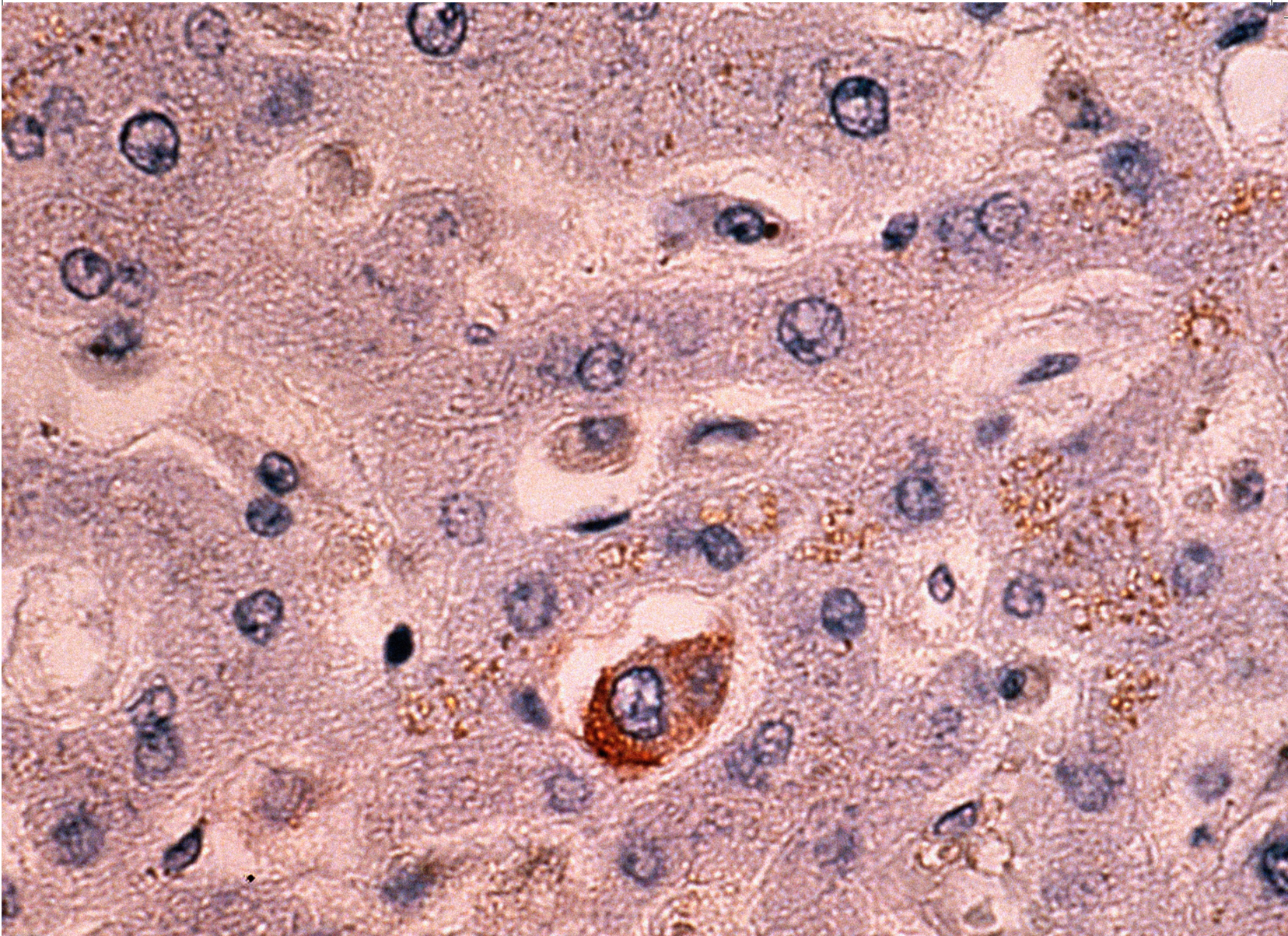
When **Max Wicha, M.D.**, transitioned from his role as the founding director of the University of Michigan's comprehensive cancer center in 2015, his accomplishments and the ongoing promise of his research were recognized with his appointment as the Madeline and Sidney Forbes Professor of Oncology, an endowed position created by the Forbes family. In June 2016, he became the founding director of the newly established Forbes Institute for Cancer Discovery, which he had worked with the family to envision and realize.

A physician-scientist recognized internationally as a cancer leader, Dr. Wicha has focused his career on the biology and treatment of breast cancer. He was part of the team that first identified breast cancer stem cells, the first such cells identified in solid tumors. This work has led to the development of several clinical trials aimed at targeting breast cancer stem cells. His team is also focused on increasing the success of immunotherapy in cancer treatment.

Dr. Wicha began his second term as the Forbes Professor in fiscal year 2020, and his time in the position has been one of great achievement. Highlights include:

- In 2016, he received a \$6.5 million Outstanding Investigator Award from the National Cancer Institute to study cancer stem cells, the small number of cells within a tumor that fuel its growth and spread; the grant is part of a program that funds projects of unusual potential in cancer research with uninterrupted funding for seven years
- He authored or co-authored more than 89 peer-reviewed publications
- He served as the 2019 Henry Russel Lecturer, considered the University of Michigan's highest honor for senior faculty members
- He continued to serve on the National Institutes of Health's 18-member Cancer Advisory Board, to which he was appointed by former President Barack Obama; the board advises the NCI director on matters related to cancer research and health policy
- In 2017, Dr. Wicha received the Stanford Medicine Alumni Association's prestigious J.E. Wallace Sterling Lifetime Achievement Award in Medicine





“Dr. Wicha’s exceptional leadership of the Forbes Institute has created a robust environment of support for the very best cancer science across the University of Michigan. We are inspired by the progress that has been made in each of the projects sponsored by the Forbes Institute.”

— ERIC FEARON, M.D., PH.D.  
EMANUEL N. MAISEL PROFESSOR OF ONCOLOGY  
DIRECTOR, ROGEL CANCER CENTER

# From Idea to New Treatment for Patients with Aggressive Brain Cancer

The Story of a Forbes Institute Grant



Daniel Wahl, M.D., Ph.D.

When Daniel Wahl, M.D., Ph.D., learned that he and a multidisciplinary team of his colleagues would receive a Forbes Institute grant in 2019, their research project was just an idea based on preliminary data showing a small insight into what made brain tumors resistant to standard chemotherapies and radiation therapy.

The plan was to catapult that data into a new way to treat glioblastoma, an aggressive brain cancer that is extremely resistant to radiation therapy. The group believed that by using a variety of laboratory-based and computational approaches they could identify common metabolic abnormalities in tumor cells. They could then target those abnormalities with a drug that could be used in combination with radiation therapy to improve outcomes.

Today, Dr. Wahl's glioblastoma patients have a new option for treatment — a clinical trial launched in the fall that is a direct result of this research.

“Because of the Forbes Institute, when I sit down with a patient to discuss treatment options, I can offer them the hope of this clinical trial,” says Dr. Wahl, an assistant professor of radiation oncology.

That clinical trial is on track to become available to patients on a much broader scale. The team applied for funding from the National Cancer Institute, scoring in the top 2% of all applications. That could mean long-term funding for the project and an expansion of the clinical trial.

Different cells within glioblastoma tumors have widely different genetic abnormalities, which has made these tumors resistant to genetically targeted drugs. Treatments that are effective regardless of the genetic abnormalities present are urgently needed. The team reasoned that drugs that target abnormal metabolism — the chemical processes that take place within cells — instead of genetic abnormalities might successfully overcome radiation treatment resistance, because they could affect most of the cells in the tumor.

Prior experiments had implicated one particular metabolic pathway, called de novo purine synthesis, as a major cause of treatment resistance in glioblastoma. The team leveraged Forbes Institute funding to measure the activity of this pathway in glioblastoma tumors in laboratory models and in patients to determine if drugs inhibiting this pathway could be useful to treat this difficult disease.

In peer-reviewed papers published in 2020, they described looking at metabolite levels within cells across dozens of genomically distinct models of glioblastoma, finding that purine metabolites, especially guanylates, are strongly related to radiation resistance. Because many of the genetic abnormalities in glioblastoma activate purine metabolism, inhibiting purine synthesis appeared to be a promising strategy to overcome therapy resistance in tumor cells with differing genetic abnormalities. In laboratory studies, they demonstrated that an FDA-approved inhibitor of purine synthesis can increase the effects of radiation, which led to the launch of the clinical trial.

“This project is remarkable,” says Eric Fearon, M.D., Ph.D., director of the Rogel Cancer Center. “The fact that the team’s National Cancer Institute grant application scored in the top 2% shows how exceptional the science is. One of the great things about the Forbes Institute is that it enables us to put our very best foot forward.”

Dr. Wahl’s partners across the University of Michigan are Sriram Chandrasekaran, Ph.D., assistant professor of biomedical engineering; Jason A. Heth, M.D., associate professor of neurological surgery; Costas A. Lyssiotis, Ph.D., assistant professor of molecular and integrative physiology; and Sriram Venneti, M.D., Ph.D., associate professor of pathology.

“We are extremely grateful for this support,” Dr. Wahl says. “It means the world to our research team, and more importantly, to our patients.”



“Funding from the Forbes Institute for Cancer Discovery was instrumental in establishing my independent research career and is directly responsible for the opening of a therapeutic clinical trial here at the University of Michigan.”

— DANIEL WAHL, M.D., PH.D.  
ASSISTANT PROFESSOR OF RADIATION ONCOLOGY

# RESEARCH PROGRESS 2020

## Using Sound Waves to Kill Cancerous Tumors Also Triggers Immune System to Fight

**H**istotripsy is a new technology developed at the University of Michigan that uses high-pressure sound waves to ablate tumors without the need for invasive surgery. In laboratory studies, we were surprised to discover that when we used this innovative technology to kill tumors with great precision, we were also teaching the immune system to recognize these tumors and reject tumor cells at distant sites.

Forbes Institute funding last year enabled us to verify that this powerful immune response takes place — and to begin to unravel how and why it takes place. We discovered, for example, that if we target the center of a tumor with histotripsy, the center of the tumor dies and the treatment stimulates an outward wave of progressive programmed cell death. The sound waves engender an immune response that gets stronger over time, reprogramming cancer cells to kill themselves.

Our work in 2020 resulted in three large grant applications that are now being evaluated by the Department of Veterans Affairs and the National Institutes of Health. We hope to earn funding on all three to further this research on a large scale. This work also has led to a national clinical trial that will be led by U-M, using the technology to treat patients with liver tumors.

While immunotherapy has shown remarkable success in some patients that have cancers recognized by the immune system, the majority of cancers are largely invisible to the immune system. To date, these cancers have not responded to immunotherapy. This research has the potential to revolutionize immunotherapy by sensitizing previously “invisible” cancers to treatment.

### COLLABORATIVE TEAM



Clifford S. Cho, M.D.  
C. Gardner Child Professor of  
Surgery



Zhen Xu, Ph.D.  
Professor of Biomedical  
Engineering

“I want to express my deep gratitude. **The forward-thinking funding that has been made available through the Forbes Institute** has been an investment that is going to pay off not just for the University of Michigan, but for all patients with cancer for years to come.”

— CLIFFORD S. CHO, M.D.  
C. GARDNER CHILD PROFESSOR OF SURGERY





“With science, you never know what you are going to find next. We are very excited, and none of this could have happened without the Forbes Institute’s backing.”

— DAVID MARKOVITZ, M.D.  
PROFESSOR OF INTERNAL MEDICINE

## In Lab Studies, New Drug Is Effective Against Cancer — and COVID-19

A very specific sugar structure is found on the surface of cells of a number of cancers and viruses such as COVID-19, but not on the surface of healthy cells. To attack this sugar and the cells that it binds to, we have molecularly modified a sugar-binding protein from bananas.

We initially found that our compound, a molecularly engineered banana lectin, was highly effective against non-small-cell lung cancer cells in laboratory studies. To pursue this significant potential, we proposed further studying the efficacy and safety of this molecule when used as an anti-cancer drug. We leveraged funding from the Forbes Institute to investigate the mechanisms by which this compound kills cancer cells without harming normal healthy cells. One unexpected discovery was that the binding molecule causes the cancer cells to eat themselves.

We also gathered data showing that our compound may be effective against breast cancer, pancreatic cancer, and liver cancer.

In the second part of our Forbes Institute project, we created a new approach to immunotherapy. In immunotherapy, immune T-cells from a patient are engineered to recognize and attack cancer. These T-cells are usually steered by antibodies. We instead made T-cells that are steered by banana lectin. We are actively engaged with collaborators at Baylor University to advance this work for lung and pancreatic cancers.

We originally designed this protein to be an anti-viral agent, so this year we tested and confirmed that it is highly active against all coronaviruses including COVID-19. Vaccines will be administered before our product can get to market, but because it is effective against all types of flu and coronaviruses, we are excited that it may help us prepare for future pandemics. The technology has been licensed by a start-up company.

### COLLABORATIVE TEAM:



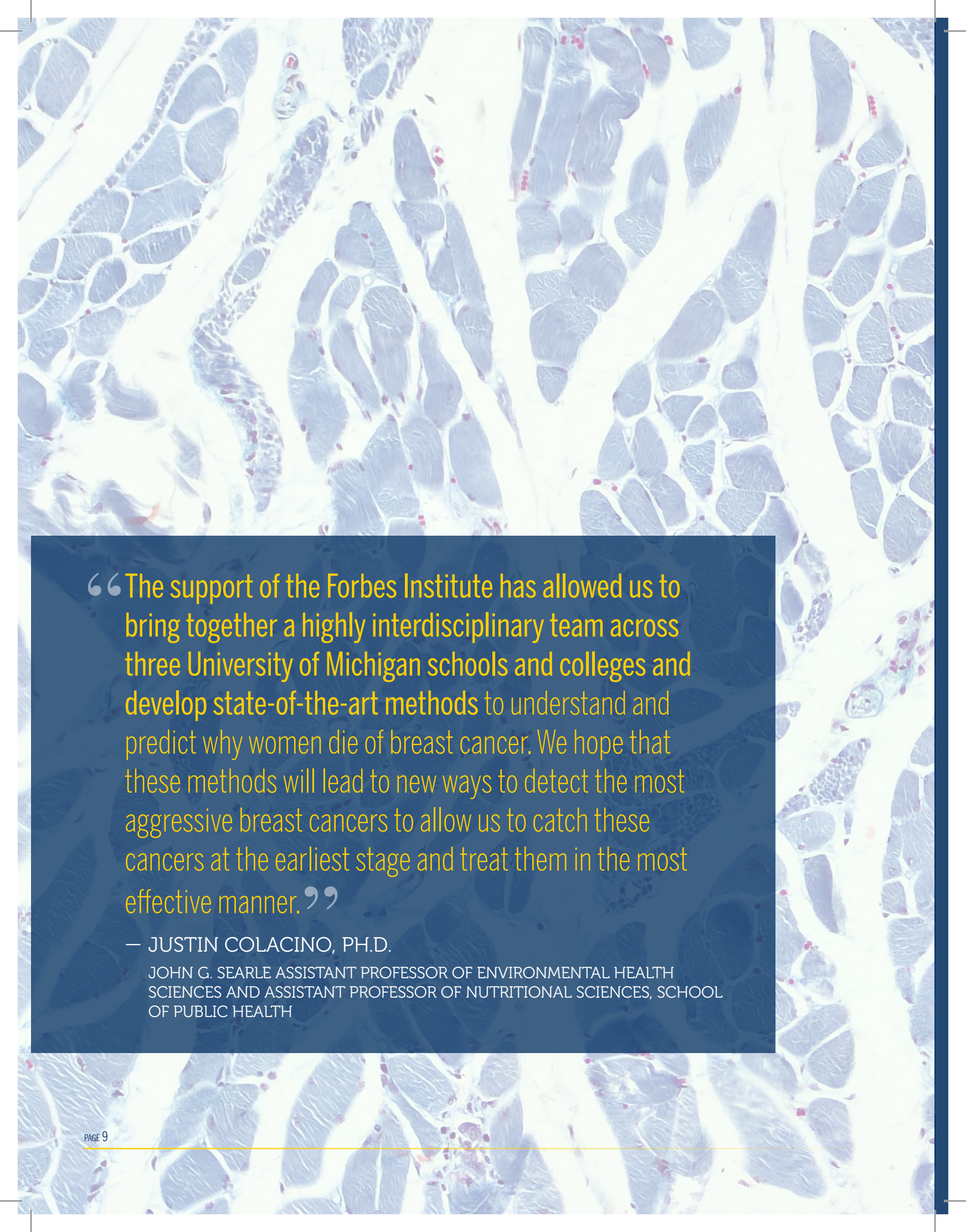
David Markovitz, M.D.  
Professor of Internal Medicine



Alnawaz Rehemtulla, Ph.D.  
Ruth Tuttle Freeman Research  
Professor of Radiation Oncology



Challice Bonifant, M.D., Ph.D.  
Assistant Professor of Oncology at  
Johns Hopkins University



“The support of the Forbes Institute has allowed us to bring together a highly interdisciplinary team across three University of Michigan schools and colleges and develop state-of-the-art methods to understand and predict why women die of breast cancer. We hope that these methods will lead to new ways to detect the most aggressive breast cancers to allow us to catch these cancers at the earliest stage and treat them in the most effective manner.”

— JUSTIN COLACINO, PH.D.

JOHN G. SEARLE ASSISTANT PROFESSOR OF ENVIRONMENTAL HEALTH SCIENCES AND ASSISTANT PROFESSOR OF NUTRITIONAL SCIENCES, SCHOOL OF PUBLIC HEALTH

# Forbes Scholars Achievements

## **Sriram Chandrasekaran, Ph.D.**

- Received a Maximizing Investigators' Research Award, National Institute of General Medical Sciences, 2020

## **David Ginsburg, M.D.**

- Elected to the American Philosophical Society, 2020
- Serves as the James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics, and Warner-Lambert/Parke-Davis Professor of Medicine

## **Jacqueline Jeruss, M.D., Ph.D.**

- Received promotion to professor of surgery, professor of pathology, and professor of biomedical engineering, 2020

## **David Markovitz, M.D.**

- Received Innovative Research Award, Rheumatology Research Foundation, 2020

## **James Moon, Ph.D.**

- Named John Gideon Searle Associate Professor, Department of Pharmaceutical Sciences, College of Pharmacy, 2018
- Received Emerging Leader Award, American Association of Pharmaceutical Scientists, 2018
- Received Mid-Career Nanotechnology Scientific Award, Applied Nanotech and Nanoscience International Conference, 2018
- Named Cellular and Molecular Bioengineering Young Innovator, 2017

## **Lonnie Shea, Ph.D.**

- Technology and Innovation Award from the Society for Biomaterials
- Serves as the William and Valerie Hall Department Chair of Biomedical Engineering and the Steven A. Goldstein Collegiate Professor of Biomedical Engineering

## **Zhen Xu, Ph.D.**

- Promoted to professor of biomedical engineering, 2020
- Received Lockhart Memorial Prize, Focused Ultrasound Foundation, 2020
- Received College of Engineering Monroe-Brown Foundation Research Excellence Award, 2020

## **Daniel Wahl, M.D., Ph.D.**

- Received Basic/Translational Science Award, American Society for Radiation Oncology Annual Meeting Abstract Awards, 2019

## See What We Can Do Together

**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 Rogel 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](https://mcancer.org/ForbesInstitute) or contact:

**Amanda Smith**

Associate Director of Development, Cancer Programs  
Michigan Medicine Office of Development

734-647-2742

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CANCER DISCOVERY**  
MICHIGAN MEDICINE

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