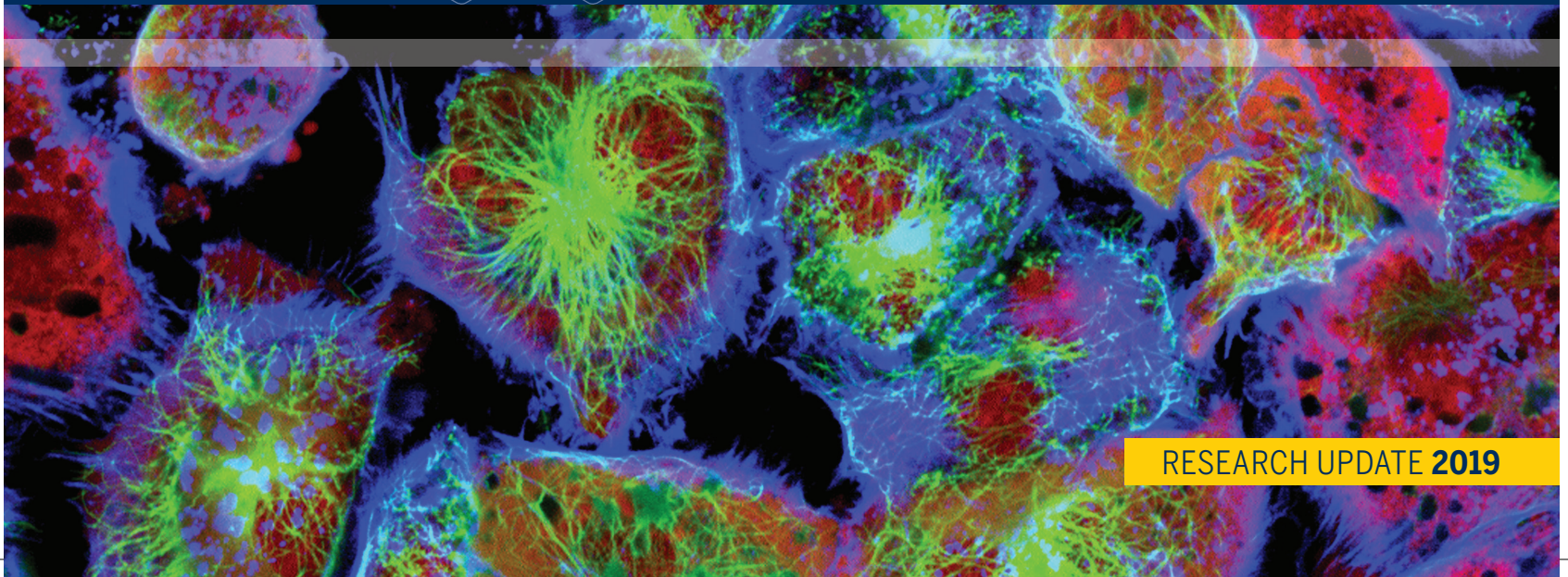




FORBES INSTITUTE FOR CANCER DISCOVERY
MICHIGAN MEDICINE



Accelerating Science Toward Cures



RESEARCH UPDATE 2019



“The bridge between research and clinical care that we have been building is creating tremendous opportunities for progress in cancer, and the Forbes Institute for Cancer Discovery is at the cutting edge. Our goal is to ensure that our discoveries make a difference in patients’ lives.” — MAX S. WICHA, M.D.

A BRIDGE TO PROGRESS

When I became a physician more than 40 years ago and sought advice about what area of medicine to go into, people who knew I wanted to combine research and clinical care warned me against choosing cancer.

At the time, a revolution was happening in basic science. Molecular biologists and geneticists were striving to understand the underlying basis of all diseases, with cancer a top priority. The problem was that there was no interaction between what was going on in the laboratory and what was going on in the clinic. They were completely different worlds.

I went against that advice and was fortunate to spend almost all of my career at the University of Michigan, where we have been leaders in breaking down those boundaries.

Fast forward to today. The bridge between research and clinical care that we have been building is creating tremendous opportunities for progress in cancer, and the Forbes Institute for Cancer Discovery is at the cutting edge. We are enabling multidisciplinary teams from departments and schools across the university — physicians, biologists, engineers, chemists, computer scientists, mathematicians, physicists, and others — to move basic science to the clinic and then back again for further understanding and growth. Our goal is to ensure that our discoveries make a difference in patients' lives.

It is a pleasure to share a report on three recently completed projects funded by the Forbes Institute. The teams' achievements in defining and leveraging new paths to treatment have the potential to greatly impact care across cancers.

Our faculty's commitment and enthusiasm is matched by the Forbes family, and it is an honor to work so closely with them to achieve our shared goals.

We appreciate your contribution to this team. Thank you for your interest and support. Please feel free to reach out to me if you have any questions about this or other cancer research.

With gratitude,

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



GRANT TITLE

An Unbiased Screen for Brain Metastasis-Promoting Gene Networks in Human Breast Cancer

RESEARCHERS

Forbes Scholar
David Ginsburg, M.D.

Stephen J. Weiss, M.D.

Identifying Genes that Help Breast Cancer Cells Spread to the Brain

To identify the critical genes that control the growth and spread of breast cancer cells, Drs. Ginsburg and Weiss used a new, unbiased DNA sequencing technique called CRISPR/Cas9 gene editing to examine every gene encoded in human DNA. Leveraging their combined expertise in genetics and the mechanisms of cancer cells, they systematically tested the effect of individually eliminating each of the approximately 20,000 known human genes from the genome of a tumor cell line. They then tested how the loss of each of these genes affected the growth of the tumor cells, both in a test tube and in breast tissue of laboratory models.

They identified a number of key genes involved in the process of breast cancer growth and metastasis, which may be targets for new treatments. These promising preliminary results are leading to further study. Their collaboration is especially focused on genes that may modulate the capacity of breast cancer cells to metastasize and proliferate within the brain.

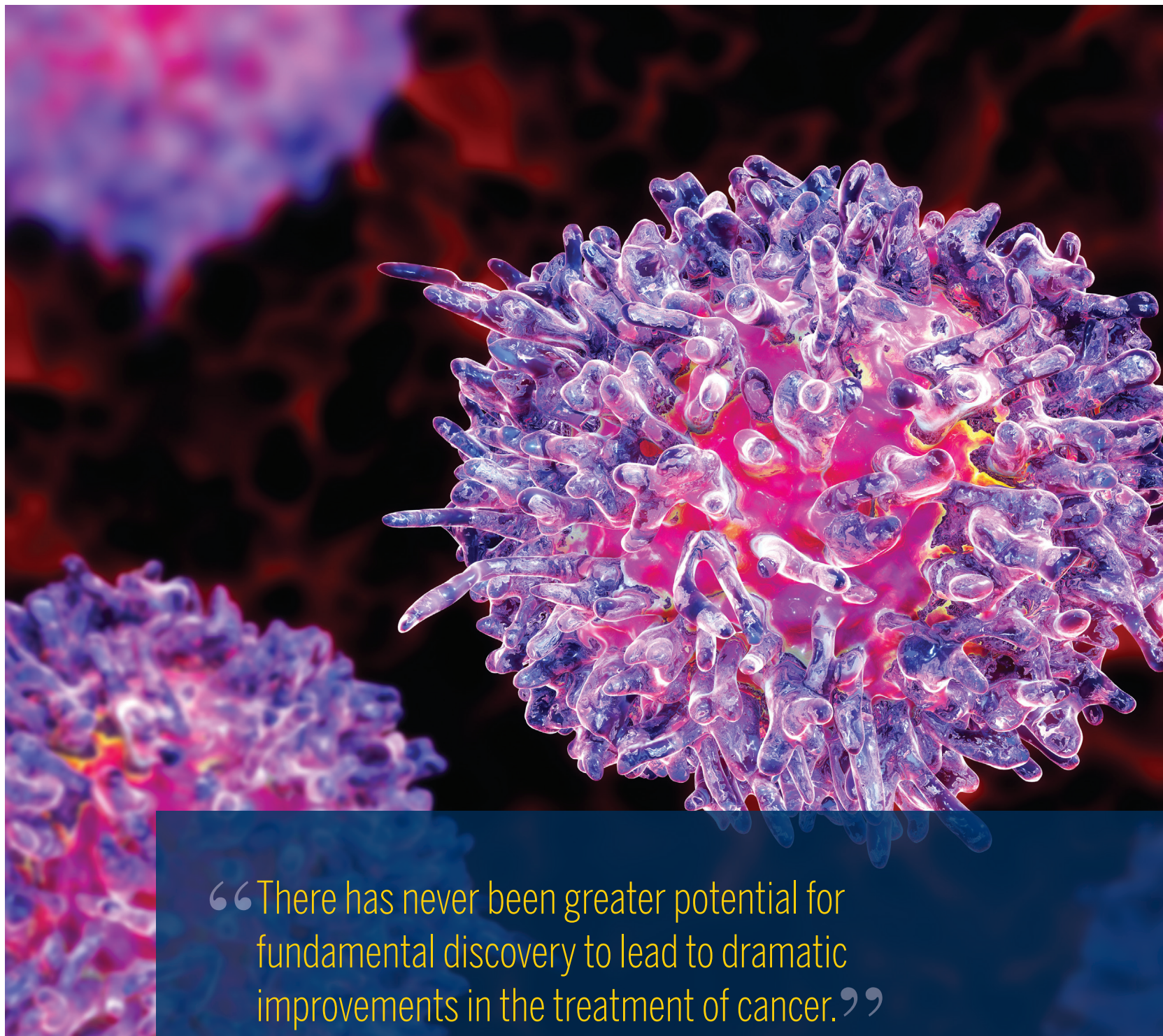
After gathering additional data, Drs. Ginsburg and Weiss anticipate applying for support from the National Institutes of Health to advance their discoveries toward therapeutic potential.



DR. GINSBURG is the James V. Neel Distinguished University Professor of Internal Medicine and Human Genetics, a Warner-Lambert/Parke-Davis Professor of Medicine, professor of pediatrics, and a research professor at the Life Sciences Institute. He has been a Howard Hughes Medical Institute investigator since 1985. As a physician, he is board-certified in hematology, oncology, internal medicine, and clinical genetics. In his lab, he investigates the fundamental biology and genetics of blood clotting. His team identified genes that may help determine the severity of the common bleeding disorder von Willebrand disease and related diseases.



DR. WEISS is the E. Gifford and Love Barnett Upjohn Professor of Internal Medicine and Oncology as well as a research professor at the Life Sciences Institute. His laboratory is focused on the mechanisms used by cancer cells, stem cells, the immune system, and vascular networks to grow, move, and build new structures like blood vessels. In cancer, he studies how cells metastasize to distant organs.



“There has never been greater potential for fundamental discovery to lead to dramatic improvements in the treatment of cancer.”

— UNIVERSITY OF MICHIGAN PRESIDENT
MARK SCHLISSEL, M.D., PH.D.

GRANT TITLE

Targeting Circulating and Disseminated Tumor Cells From Pre-Invasive Breast Tumors

RESEARCHERS

Forbes Scholar
Justin Colacino, Ph.D., MPH
Dean E. Brenner, M.D.

Defining a New Paradigm for Breast Cancer Detection, Tracking, and Treatment

Breast cancer is traditionally thought to progress through a continuum from normal breast tissue through several stages to locally invasive cancer and then to metastatic disease. A growing number of studies challenge the conventional wisdom of this linear progression, showing that metastasis can occur and that women can die from breast cancer without ever having had a breast tumor. Metastasis is one of the greatest challenges in treating breast cancer.

Dr. Colacino, an expert in breast stem cells and the early stages of cancer, and Dr. Brenner, an expert in the biology of the progression of invasive cancer, are testing the idea that systemic tumor cell dissemination may precede local invasion in breast cancer and that early tumor cells have stem-cell-like characteristics.

The funding from the Forbes Institute enabled the team to do early-stage studies. They used state-of-the-art approaches to investigate circulating tumor cells from patients with identifiable pre-invasive breast lesions. They demonstrated that circulating tumor cells are detectable in patients who have abnormal cells in the breast but do not have locally invasive breast cancer. This suggests that metastasis can occur before or at the same time as breast cancer tumors.

Their findings could help create a paradigm shift in prevention, diagnosis, and treatment:

- Breast cancer detection may move to identifying lesions at risk for invasion/ dissemination
- New therapies may target the dissemination of cells and disseminated cell populations
- Monitoring disease progression may shift to tools that track circulating tumor cells and other circulating markers
- Prevention research and practice may explore how modifying diet, the microbiome, and exercise impacts the dissemination of circulating tumor cells.

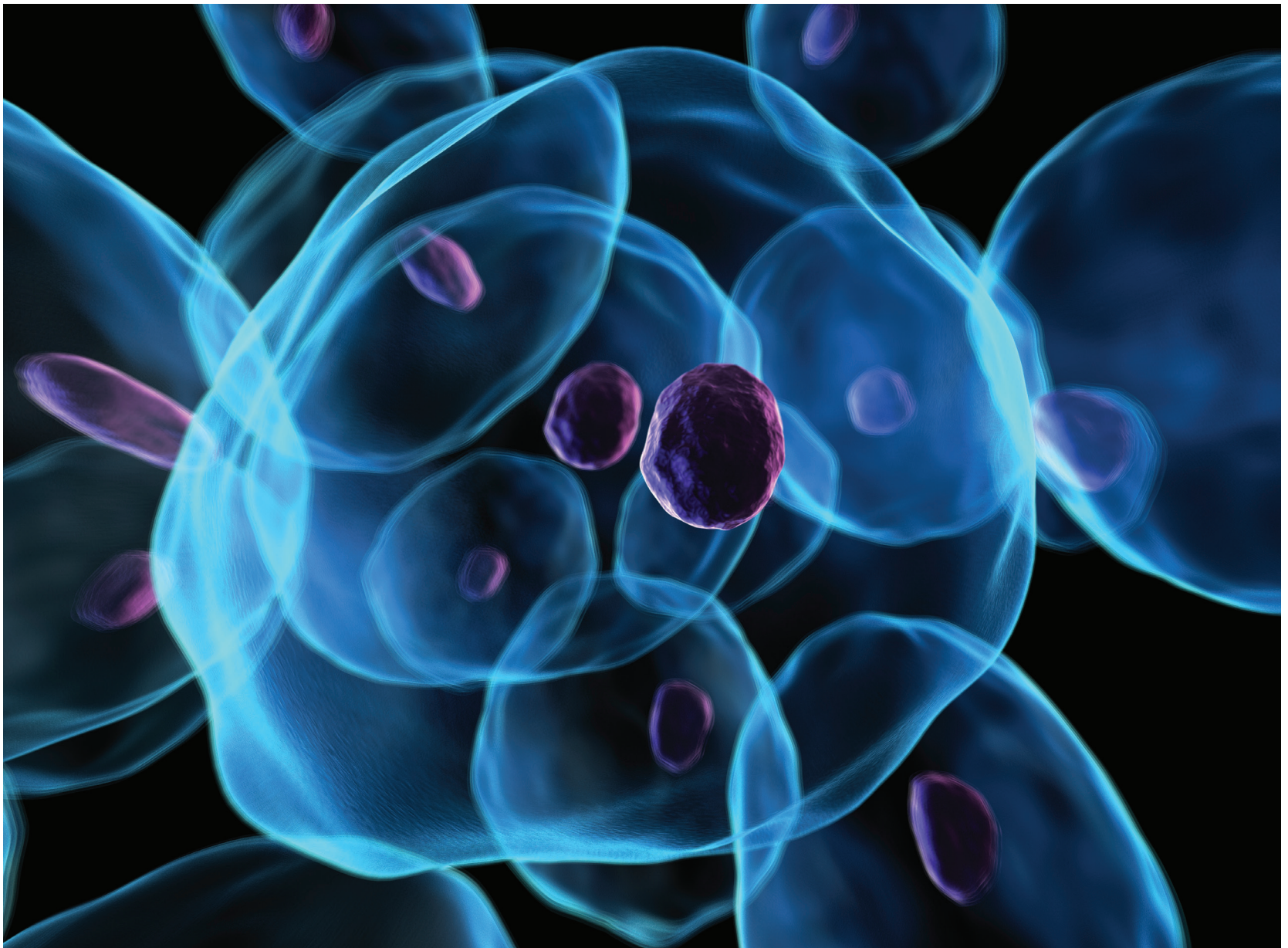


DR. COLACINO is the John G. Searle Assistant Professor of Environmental Health Sciences and an assistant professor of nutritional sciences in the School of Public Health. His research focuses on understanding the dietary factors in the development of cancer and cancer prevention. His research merges laboratory studies with the statistical analysis of large-scale genomic studies and epidemiologic data sets.



DR. BRENNER is the Moshe Talpaz, M.D., Professor of Translational Oncology and a professor of pharmacology and internal medicine. His research focuses on cancer prevention, biomarker discovery and validation, hepatic metabolism of drugs, drug interactions, effects of disease states on drugs, and pharmacology.

The team has engaged a talented cohort of experts in the project, including Max Wicha, M.D., the Madeline and Sidney Forbes Professor of Oncology, director of the Forbes Institute for Cancer Discovery, and an international leader in breast cancer stem cells; Jacqueline Jeruss, M.D., Ph.D., an associate professor of surgery, pathology, and biomedical engineering, as well as director of the U-M Breast Care Center and an expert in breast cancer metastasis and treatment; Celina Kleer, M.D., the Harold A. Oberman Collegiate Professor of Pathology, director of the Breast Pathology Program, and an expert in the mechanisms of breast cancer invasion and metastasis; and Sunitha Nagrath, Ph.D., an associate professor of chemical engineering and developer of breakthrough circulating tumor cell capture devices. They also have developed a partnership with a research team in India to broaden the scope and accelerate the pace of what they can learn.



GRANT TITLE

Targeting YEATS4 chromatin reader in cancer

RESEARCHERS

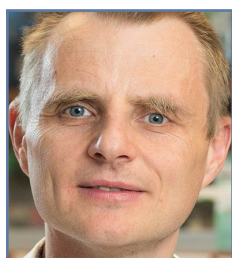
Forbes Scholar
Tomasz Cierpicki, Ph.D.
Jolanta Grembecka, Ph.D.
Venkateshwar Keshamouni, Ph.D.

Forging a New Path to Treatment for Lung and Other Cancers

An interdisciplinary investigation of an oncogene involved in non-small-cell lung cancer, glioblastoma, colon cancer, sarcomas, and pancreatic cancer has successfully led to the identification of chemical agents that can block the gene's activity and potentially block the proliferation of cancer cells that depend on the gene. Leveraging funding from the Forbes Institute, Drs. Cierpicki, Grembecka, and Keshamouni have completed proof-of-concept studies demonstrating that the pharmacological inhibition of oncogene YEATS4 could benefit patients with cancer.

To identify and develop the inhibitors, the team used a method called fragment-based drug discovery, in which they screen very small molecules, or fragments, of compounds to identify starting points for their work. They then evaluated the compounds using a variety of technologies to determine the atomic structure of the molecules, their binding affinity and activity in non-small-cell lung cancer, and more.

The team has published a manuscript describing YEATS4 interactions. They are applying for a patent protecting the intellectual property for YEATS4 inhibitors and have submitted a National Institutes of Health grant application for funding to advance the project. Next steps include optimizing the properties of the inhibitors and moving toward first-in-human clinical trials.



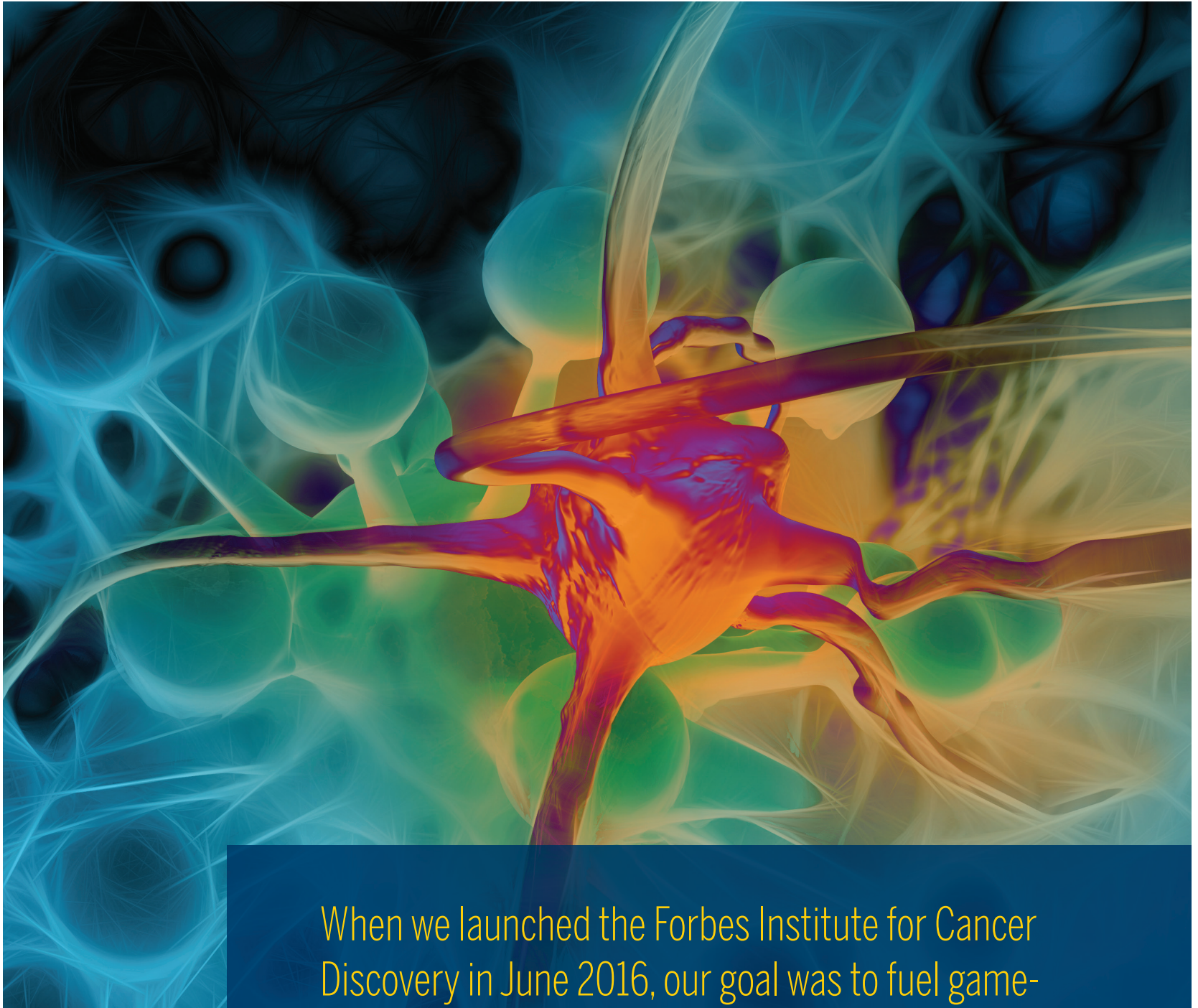
DR. CIERPICKI is an associate professor of biophysics in the College of Literature, Science, and the Arts, as well as an associate professor of pathology. He researches cancer-associated proteins and develops small molecule inhibitors that target them. His laboratory has developed first inhibitors of the menin-MLL interaction as a new potential therapeutic strategy in leukemias.



DR. GREMBECKA is an associate professor of pathology focusing on the discovery and development of small molecules that can block the growth and spread of cancer by interfering with proteins involved in cancer cell division and spread. She also has been focusing on proteins in leukemias.



DR. KESHAMOUNI is an associate professor of internal medicine in the Division of Pulmonary and Critical Care Medicine. His research group is investigating biological mechanisms that may help tumor cells in lung cancer multiply and spread — and identifying molecular targets that can mediate these mechanisms for the prevention and treatment of lung cancer.



When we launched the Forbes Institute for Cancer Discovery in June 2016, our goal was to fuel game-changing initiatives that would drive breakthroughs in cancer research. Today, our multidisciplinary projects are yielding exciting and promising results.



“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



See What We Can Do Together

Join us! The Forbes Institute for Cancer Discovery was founded by Sidney and Madeline Forbes, long-time 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 or contact:

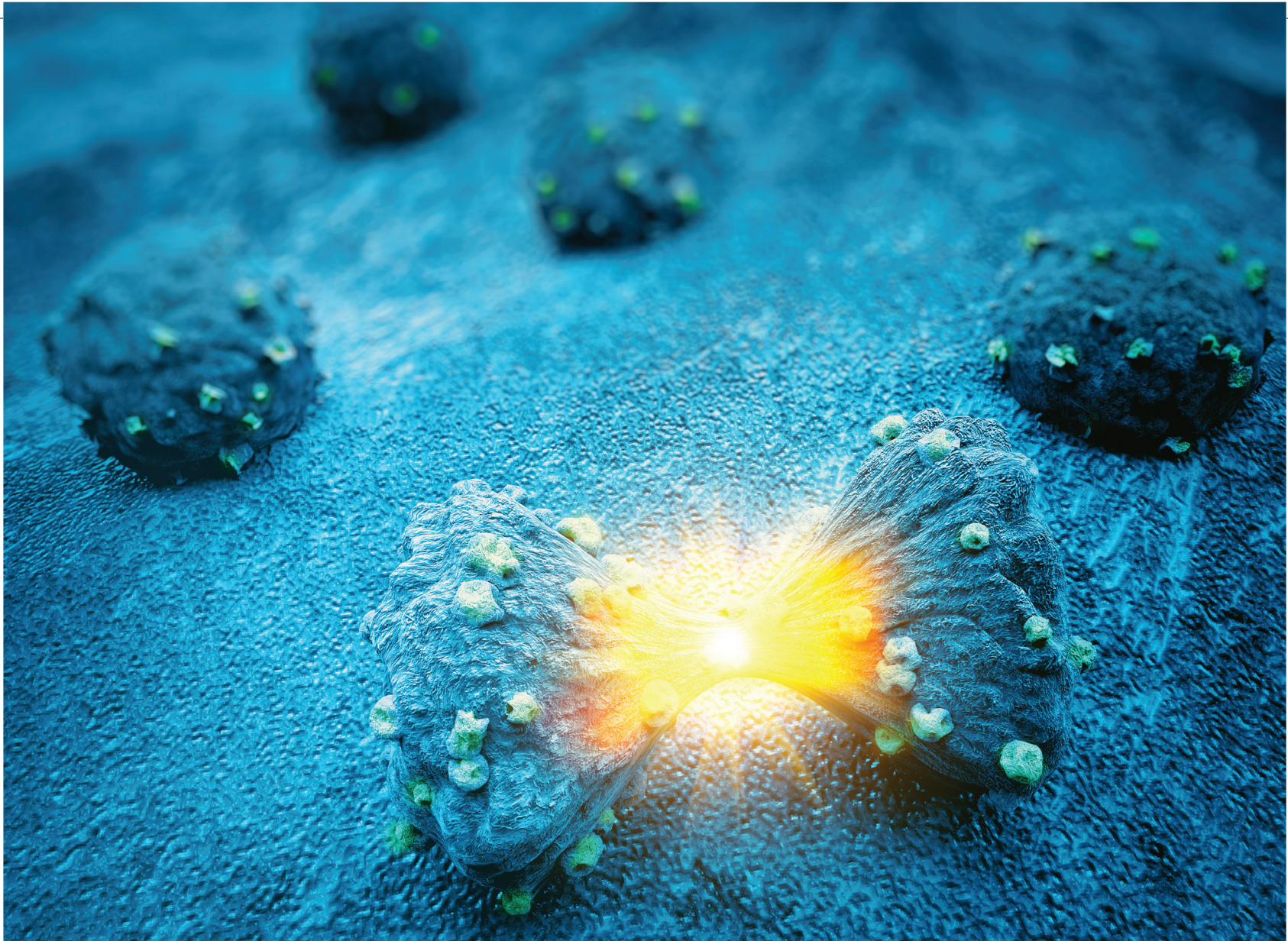
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