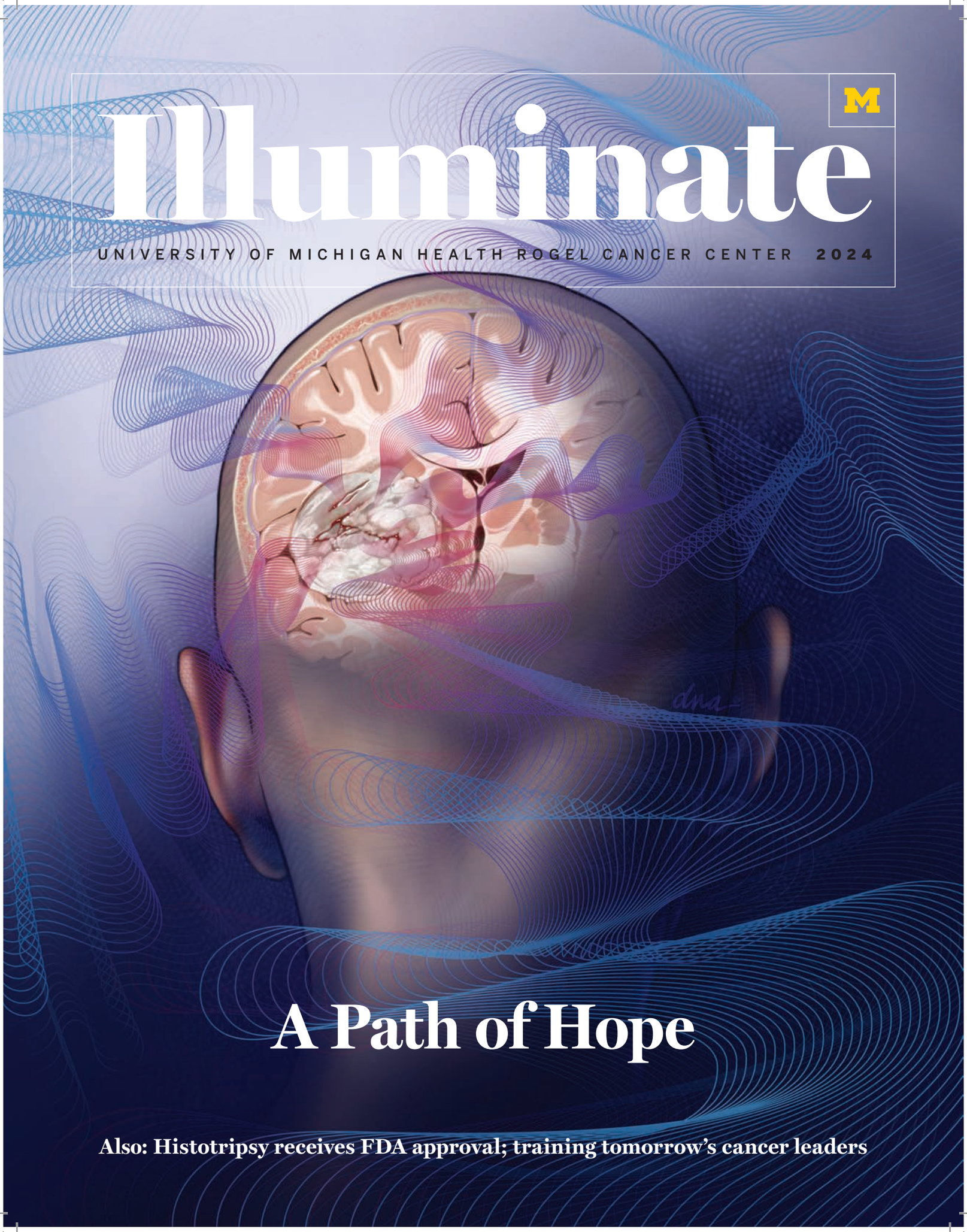
Illuminate

UNIVERSITY OF MICHIGAN HEALTH ROGEL CANCER CENTER 2024



A Path of Hope

Also: Histotripsy receives FDA approval; training tomorrow's cancer leaders

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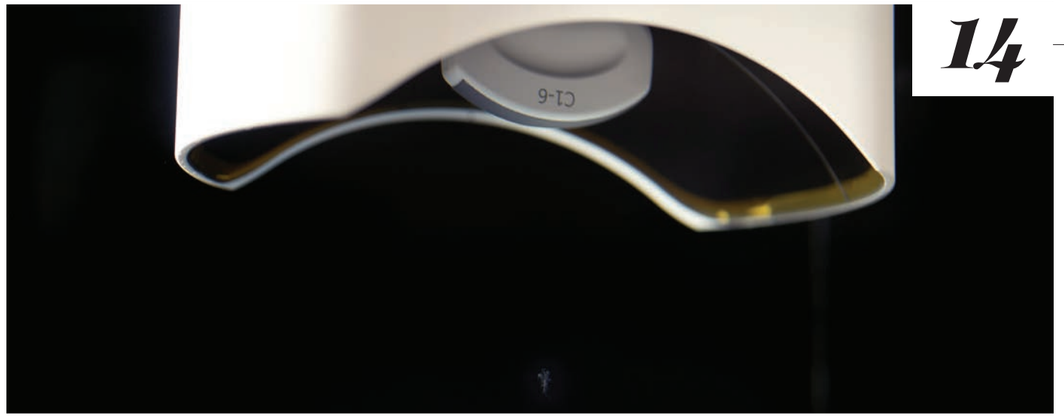

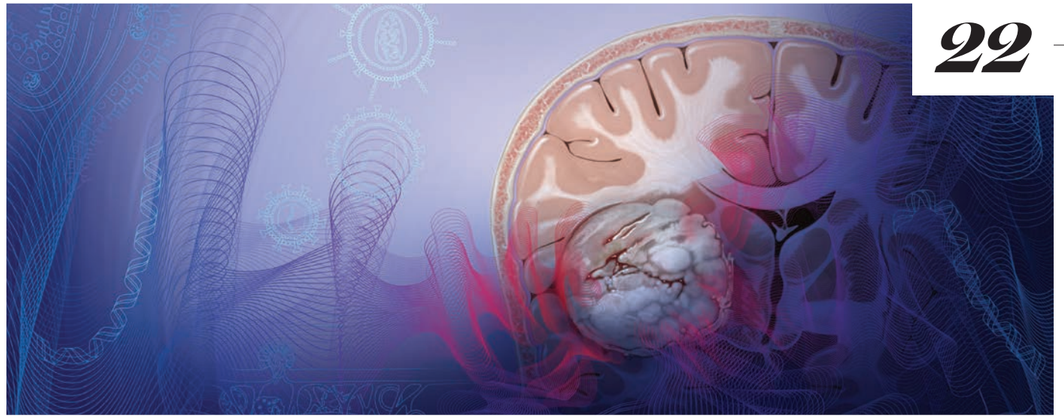

FEATURES

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ROGEL CANCER CENTER
UNIVERSITY OF MICHIGAN HEALTH

About Us

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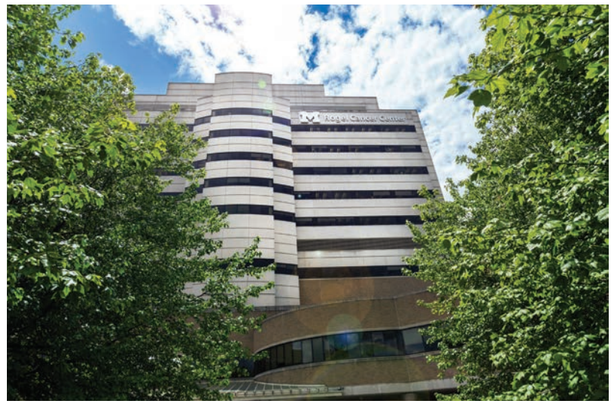
and **54** departments

1,000 annual publications

1,600 yearly clinical trial accruals

$174M grant funding

No. 11 National Cancer Institute funding



Director's Letter

Dear Colleagues,

The last year has been filled with opportunities that reflect who we are as a cancer center, how far we've come, and where our focus must be to achieve major advances for patients and survivors, their families and all at risk of cancer. In 2023, we successfully renewed our Cancer Center Support Grant from the National Cancer Institute and we now begin our 40th year of continuous NCI support. I am enormously proud of our Rogel community, who day in and day out engage in innovative research and compassionate care while also training the next generation of cancer pioneers and serving communities across Michigan and beyond.

The NCI grant review process also shed light on ways we can improve our work. With our five-year strategic plan and guidance from internal and external advisory groups, we're charting our path forward, including enhancing our research and training efforts, broadening our commitment to diversity, equity, inclusion and justice, and refining how we improve cancer care and outcomes at our institution and in the communities we serve.

As I reflect on this moment, I'm struck by a refrain that guides us in our research: Follow the science. The very nature of research requires comfort with and appreciation for the unknown, curiosity and commitment to dig deep, and flexibility to change course when needed. As researchers, we rely on being open to where the science takes us and being nimble, creative and resilient. Our ability to value new information as it comes to light, to recognize its significance and make unexpected connections offers us a path as we move into Rogel's next phase. Because of our team-based culture that unites members from across nine schools and 50-plus departments, we have unique opportunities to make significant discoveries and to translate new concepts, agents and approaches to improve outcomes and quality of life.

This is the fourth issue of *Illuminate*, our research magazine that tells the story of who we are at Rogel. This year's pages are filled with stories of following the science, of findings that took researchers to unanticipated places, of career paths rooted in discovery, of decades-long work that led to breakthroughs for patients. In this issue, you'll read about a professor who began her work in graduate school to find a completely non-invasive, non-thermal ultrasound that could be used to destroy tumors, and how her dedication, collaboration and willingness to be led to new areas of discovery culminated in FDA approval. You'll also read about a team advancing brain cancer research and in doing so creating a hub of innovation at Rogel for this aggressive and often untreatable disease.

The third feature interprets following the science from a community standpoint, telling the story of education programs Rogel offers for young scientists. Here, we see how the path to a career in cancer is filled with mentorship and guidance, and how especially connecting with those students who wouldn't otherwise be exposed to lab work or hands-on experiments aligns with our values as an institution.

Following the science implies a certain amount of mystery, a dynamic relationship between us as researchers and the unknown. As we think about the future of Rogel, the areas in which we want to grow, the new colleagues we hope to engage in our mission, we trust that an open, inquisitive and reflective mind will guide us to further innovation, collaboration and a positive impact for all at risk of or affected by cancer.

Sincerely,

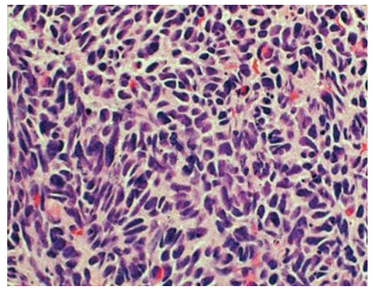
Eric Fearon, M.D., Ph.D.
Director, University of Michigan Health Rogel Cancer Center
Emanuel N. Maisel Professor of Oncology

Photo: Erica Reist Bass

Discoveries

Photo: Leisa Thompson

STUDY SHOWS NEW APPROACH TO TARGET DEADLY FORM OF PROSTATE CANCER



A STUDY FROM ROGEL uncovers a new mechanism to explain why some prostate tumors switch from a common, treatable form to a more rare and aggressive form of prostate cancer.

Using tissue samples and cell models from patients, **Joshi Alumkal, M.D.**, Wicha Family Professor of Oncology and leader of the genitourinary medical oncology section at Rogel, and his team zeroed in on the lysine specific demethylase 1, a protein involved in turning genes off and on in normal and cancer cells that appears particularly important in certain aggressive forms of prostate cancer.

Further, they outlined a promising path to overcome this deadly form of treatment resistance: LSD1 inhibitors. The findings are published in *JCI Insight*.

"Our laboratory is focused on understanding how prostate tumors shift away from a glandular program and ways to block this lineage switch," says Alumkal, who also co-leads the Translational and Clinical Research Program at Rogel. ➔

EARLY FINDINGS SUGGEST CLINICAL AND LAB-BASED APPROACH CRITICAL TO TRACKING HEAD AND NECK CANCER RECURRENCE

EARLY FINDINGS OF TWO ROGEL STUDIES shed light on new ways to anticipate recurrence in HPV-positive head and neck cancer sooner. The papers, published in *Cancer* and *Oral Oncology*, offer clinical and technological perspectives on how to measure if recurrence is happening earlier than current blood tests allow, and provide a framework for a new, more sensitive blood test that could help in this monitoring.

"When metastatic head and neck cancer returns, it impacts quality of life and can be disfiguring, interfering with the ability to talk, swallow and even breathe," says **Paul Swiecicki, M.D.**, associate medical director for the Oncology Clinical Trials Support Unit at Rogel.

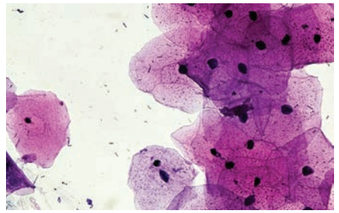
The studies aim to identify different clinical ways that providers can more strategically track for recurrence and offer a newly developed test to better detect blood biomarkers.

Muneesh Tewari, M.D., Ph.D., says this is a step towards a more proactive approach to tackling recurrence in head and neck cancer. "As of now, we only have the tools to react to symptoms when they recur. We want to find a way to be able to detect what's causing the symptoms much, much sooner, even before the symptoms appear."

NERVE DENSITY LINKED TO ORAL CANCER OUTCOMES

RESEARCHERS IDENTIFIED A NEW METRIC to articulate the relationship between nerve density and oral cancer. The study, published in *Clinical Cancer Research*, investigated normalized nerve density to translate previous mechanistic studies into a context that could be used in the clinic.

"We are recognizing more and more that there's a very dynamic interaction between nerves and cancer cells in the tumor microenvironment," says **Nisha D'Silva, B.D.S., M.S.D, Ph.D.**, Donald Kerr Endowed Collegiate Professor of Oral Pathology and senior author.



"We showed that tumors with high normalized nerve density seem to be associated with poor survival for patients with tongue cancer, which is the most common type of oral cancer," D'Silva continues. "We also found that patients with high normalized nerve density and a smaller distance between the nerve and the tumor have poorer outcomes."

ANALYSIS OF DONOR PANCREAS DEFINES THE TRANSCRIPTOMIC SIGNATURE AND MICROENVIRONMENT OF EARLY NEOPLASTIC LESIONS

THE ADULT HEALTHY HUMAN PANCREAS has been poorly studied wgiven the challenge of obtaining pancreas tissue. Rogel researchers obtained pancreata from brain dead donors who were diverse in age and race and had no known pancreas disease.

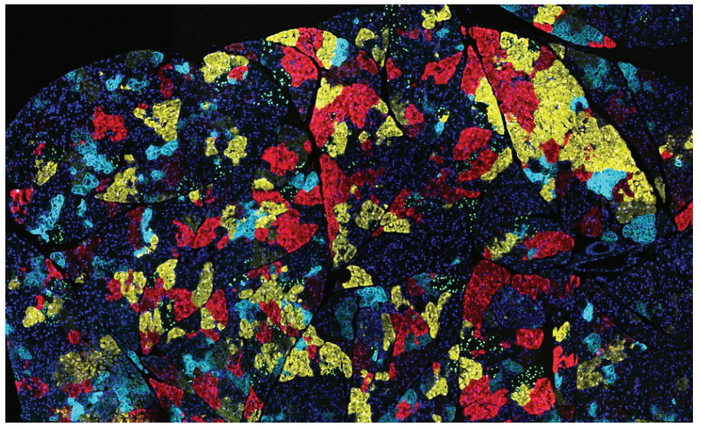
Analysis of the samples revealed pancreatic intraepithelial neoplasia (PanIN) lesions in most individuals regardless of age. Using a combination of multiplex IHC, single-cell RNA sequencing and spatial transcriptomics, researchers led by **Marina Pasca di Magliano, Ph.D.**, provide the first-ever characterization of the unique microenvironment of the adult human pancreas and sporadic PanIN lesions. These findings were featured in *Cancer Discovery*.

STUDY BRINGS INSIGHT TO KIDNEY CANCER WITH GENE MUTATION

FINDINGS FROM OVER 800 CLINICAL ASSAYS performed for kidney patients with MiTF family gene mutations, the largest series of its kind in kidney cancer, carries deep clinical and diagnostics implications. The study is published in the *American Journal of Clinical Pathology*.

The team, led by **Rohit Mehra, M.D.**, performed over 800 clinical assays on the MiTF family genes TFE3 and TFEB in renal tumors with morphologic and biomarker alterations considered suspicious for MiTF family genetic mutations.

The findings show that patients who had renal tumors with TFEB amplification were significantly older than patients with renal tumors housing TFE3 or TFEB translocation.



STUDY FINDS CANCER CELLS USE A NEW FUEL IN ABSENCE OF SUGAR

RESEARCHERS DISCOVERED A NEW NUTRIENT source that pancreatic cancer cells use to grow. The molecule, uridine, offers insight into both biochemical processes and possible therapeutic pathways.

The findings, published in *Nature*, show that cancer cells can adapt when they don't have access to glucose. Researchers have previously identified other nutrients that serve as fuel sources for pancreatic cancer; this study adds uridine to the catalog.

Pancreatic tumors have few functioning blood vessels and can't easily access nutrients that come from the bloodstream, like glucose. **Costas Lyssiotis, Ph.D.**, Maisel Research Professor of Oncology, explained that without the right nutrients, the cancer cells get hungry. "We know they still grow, obviously, but what are they using to grow?" he says. "These findings show that, under certain circumstances, uridine is one of those fuels."

SEX, AGE, MENTAL HEALTH AND MORE CAN AFFECT PERCEIVED BARRIERS TO GENETIC TESTING FOR CANCER

IN A STUDY led by **Jennifer Griggs, M.D., M.P.H.**, **Elena Stoffel, M.D., M.P.H.**, and **Ken Resnicow, Ph.D.**, women were more likely to report worries about the implications of their genetic test results for family members and how their results could affect their health and life insurance.

Age, time since cancer diagnosis, having a child, having depression and having a cancer related to a BRCA gene also affected patients' concerns around genetic testing. The researchers correctly predicted the majority of these factors.

Yet the researchers also found that the motivations for patients to undergo genetic testing were not associated with any of the factors they studied, except for identifying as female (women could better foresee the health benefits of genetic testing, including an understanding that knowing their genetic status could help them plan their cancer treatment and increase their sense of personal control.)

"The reasons individuals are motivated to pursue genetic testing may be particularly personal, and current research may not have captured them appropriately," says first author **Erika Hanson**, a clinical research coordinator for the Michigan Genetic Hereditary Testing, or MiGHT, trial. The study was published in *Cancer Medicine*.

FREE ONLINE TOOL HELPS PROSTATE CANCER PATIENTS SAVE ON OUT-OF-POCKET DRUG COSTS

A FREE ONLINE TOOL could potentially save some prostate cancer patients more than $9,000 in out-of-pocket drug costs, a study finds. For patients enrolled in Medicare Part D prescription drug plans, out-of-pocket costs can vary significantly.

But by using an online Medicare plan finder tool, patients can compare pricing among all Part D drug plans offered in their area and select the most affordable plan.

Rogel researchers found that the Medicare Part D Plan Finder, which is funded by the Centers for Medicare and Medicaid Services, can identify significant savings for patients taking abiraterone or enzalutamide, two common prescription drugs for advanced prostate cancer. The study is published in *Urology Practice*.

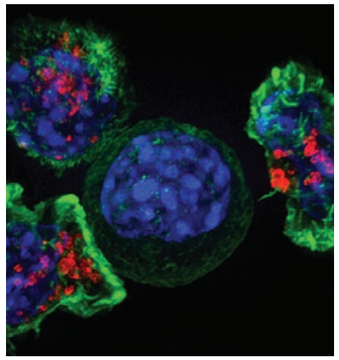
"Patients with Medicare Part D have dozens of different drug plans available to choose from, but most patients unfortunately are not aware of this. If they compare estimated costs, they could save thousands of dollars each year in drug costs. This could make a huge impact for patients with limited resources," says lead study author **Benjamin Pockros, M.D., M.B.A.**, a urology resident at Michigan Medicine. ➔

CERTAIN GENE SIGNALING REWIRES TUMORS AFTER IMMUNOTHERAPY

RESEARCHERS HAVE FOUND A MECHANISM for why a subset of patients' tumors grow, rather than shrink, when faced with immunotherapy.

Immunotherapy has been a major advancement in cancer therapy, but it is not effective for all patients. In some instances, it can even cause tumors to "hyperprogress."

Rogel researchers **Weiping Zou, M.D., Ph.D.**, and **Michael D. Green, M.D., Ph.D.**, used tumor samples from patients as well as mouse models to investigate the molecular pathways involved when immunotherapy worsens, instead of slows, the progress of disease. The study was published in *Cancer Cell*.



They found that tumors with hyperprogression after immunotherapy exhibited elevated levels of fibroblast growth factor 2, known as FGF2, and beta-catenin signaling. Further, the mouse models showed that the gene signaling interferon gamma derived from CD8+ T cells, leads to hyperprogression of disease by rewiring the tumors' metabolic pathways.

STUDY OFFERS CLUES TO HOW CANCER SPREADS TO THE BRAIN

WHEN CANCER SPREADS TO THE BRAIN, treatment options fall off. Most of the drugs designed to target metastases do not cross the blood-brain barrier or are ineffective at treating brain metastases.

"Understanding how cancer cells thrive or fail in the brain niche could help us develop new treatments targeting these molecular processes," says **Sofia Merajver, M.D., Ph.D.**, the Greater Good Breast Cancer Research Professor.

To understand the molecular processes that influence how cancer cells pass through the blood-brain barrier, Merajver and colleagues used two microfluidic chips that mapped cancer cell migration to the brain and looked at what was happening in the blood-brain niche. Results are published in *Advanced NanoBiomed Research*.

Photo: Edda Pacifico

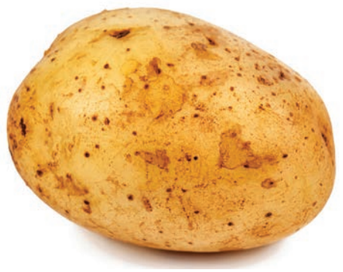
POTATO STARCH SUPPLEMENTS COULD BE SOLUTION TO BONE MARROW TRANSPLANT COMPLICATIONS

ROGEL EXPERTS HAVE FOUND a potential solution for preventing a common and dangerous complication in patients that receive stem cell transplants from a donor's blood or bone marrow.

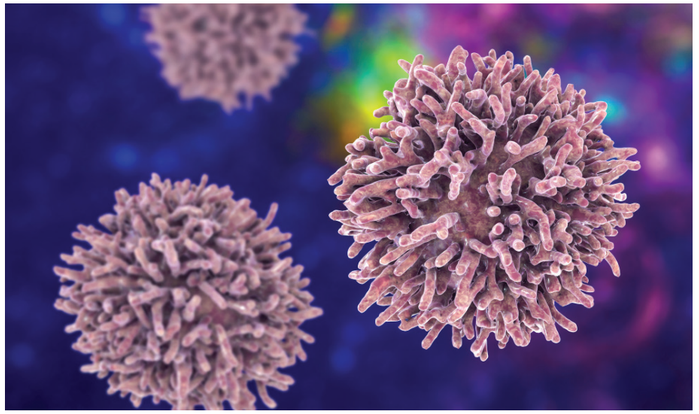
Approximately 18,000 people per year in the United States are diagnosed with life threatening illnesses, including blood cancers where a blood or bone marrow stem cell transplant from a donor is their best treatment option.

When patients receive a stem cell transplant, they get a new immune system from the donor whose job is to attack cells that don't belong there, including cancer cells.

"Graft versus host disease is a major limitation to the lifesaving capability of blood or marrow stem cell transplants. It is exciting to think of the prospect of potentially finding a simple, low-cost, and safe approach to mitigating this dangerous complication for patients who need a stem cell transplant, but researching this approach in more patients is still needed to confirm," says **Mary Riwes, D.O.**, assistant professor of internal medicine.



Photos: Getty Images



A 'TRANSFORMATIONAL TIME' FOR THYROID CANCER

AFTER YEARS IN THE SHADOW of more common cancers, there's new light for patients with thyroid cancer.

"It's been a transformational time for thyroid cancer," says **Megan R. Haymart, M.D.**, Nancy Wigginton Endocrinology Research Professor of Thyroid Cancer.

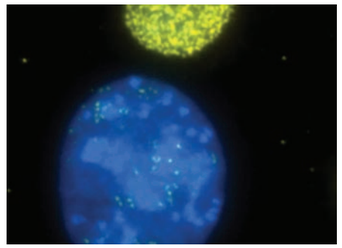
Increased use of neck ultrasounds has driven up the number of people globally who are diagnosed with thyroid cancer, which has brought new attention to the disease. It's now the ninth most common cancer worldwide.

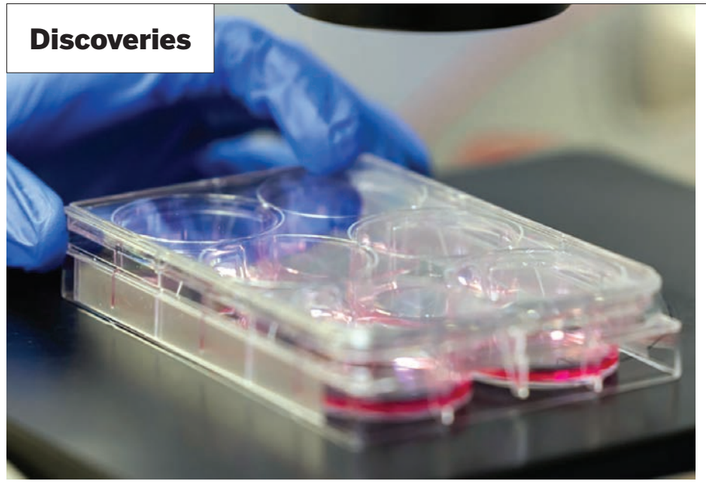
Haymart was invited to assemble an international team of authors to take on one of the Lancet's Clinical Practice topics. The team started with a seminar paper on thyroid cancer and will continue to alert the journal to practice-changing research over the next four years.

HIGH LEVELS OF AMMONIA IN COLON TUMORS INHIBITS T CELL GROWTH AND RESPONSE TO IMMUNOTHERAPY

HIGH LEVELS OF AMMONIA in tumors leads to fewer T cells and immunotherapy resistance in mouse models of colorectal cancer, new findings from Rogel revealed. Researchers found that ammonia inhibits the growth and function of T cells, which are vital for anti-tumor immunity. The findings appear in *Cell Metabolism*.

"We identified the mechanism of how ammonia dysregulates T cell function and showed that reducing ammonia levels using FDA-approved drugs for hyperammonemia can reduce tumor size in several different models including metastatic colorectal cancer," says **Hannah Bell, Ph.D.**, a postdoctoral fellow in cancer biology and author on this paper. "Use of this drug also synergizes with immunotherapy. If you treat the mice with immunotherapy when you also treat them with this ammonia reducing agent, you're able to sensitize the tumors to treatment." ➔





‘CELL FOOD’ GIVES INSIGHT INTO T CELL METABOLISM

THE METABOLIC PATHWAYS that make a specific type of T cell function are different than previously believed, researchers found. The key to this discovery lies in a new methodology developed by graduate student **Hanna Hong** and **Costas Lyssiotis, Ph.D.**, authors of a study in Science Immunology, in *Science Immunology*.

T cells are critical players of adaptive immunity that protect against infections and cancers. Metabolic pathways produce the energy and building blocks required for them to carry out their jobs. “A T cell’s specific identity and function are ruled by metabolic pathways, so each type of T cell’s inner workings are distinct,” Hong explains.

For this study, Hong developed a type of “cell food” to grow T cells in culture that look and behave like the T cells in an organism. She focused on a specific type of T cell called TH17, which act in the body’s immune response to pathogens.

“Because TH17 cells can have different metabolic pathways, they have the capacity to take on properties of other types of T cells that are associated with autoimmunity and immune suppression,” Hong says. “We’re dedicating more effort to understanding the underlying mechanisms that cause TH17 cells to transition from those that protect against infections to those that promote autoimmunity. Ultimately, the hope is that targeting these pathways can reverse disease.”

RESEARCHERS USE A NEW APPROACH TO HIT AN ‘UNDRUGGABLE’ TARGET

THE PROTEIN STAT5 has long been an appealing target against cancer, but after decades of research it was consigned to the “undruggable” category. Now, Rogel researchers have found success with a new approach.

By tapping into a cellular garbage disposal function, researchers found they could eliminate STAT5 from cell cultures and mice, setting the stage for potential development as a cancer treatment.

Shaomeng Wang, Ph.D., Warner-Lambert/Parke-Davis Professor in Medicine, and team identified a protein degrader, AK-2292, that targets and removes STAT5. The compound was highly specific to STAT5 with no effect on other STAT proteins. It was effectively taken up by both cell lines and mouse models and was found to stop cell growth in cell lines of human chronic myeloid leukemia and to induce tumor regression in mouse models of CML. Results are published in *Nature Chemical Biology*.

CHANGING THE WAY IMMUNE-BASED CANCER DRUGS ARE DELIVERED COULD REDUCE COSTS BY 14%

AN ANALYSIS FINDS THAT UP TO MILLIONS OF DOLLARS could be saved annually on cancer immunotherapy treatments across the Veterans Health Administration by reconsidering how those drugs are delivered.

It’s a concept that could be applied to all cancer centers nationwide. Immune checkpoint inhibitors were initially tested and approved at weight-based dosages but then moved to one-size-fits-all flat doses, in part to reduce drug waste.

But in a study published in *Health Affairs*, Rogel researchers found that if vials intended for a single patient’s use are shared across patients, then physicians could deliver customized doses while also reducing waste and costs.

“Administering drugs in flat one-size-fits-all dosages is predictable and allows for single-use vials with less drug material being discarded. This gives the appearance of less waste to the payer,” says **Garth W. Strohbehn, M.D., M.Phil**. “But it conceals the fact that excess drug amounts may be administered to the patient, relative to what they need, which ultimately may be increasing usage and drug spending.”

METABOLITE TELLS CELLS WHETHER TO REPAIR DNA

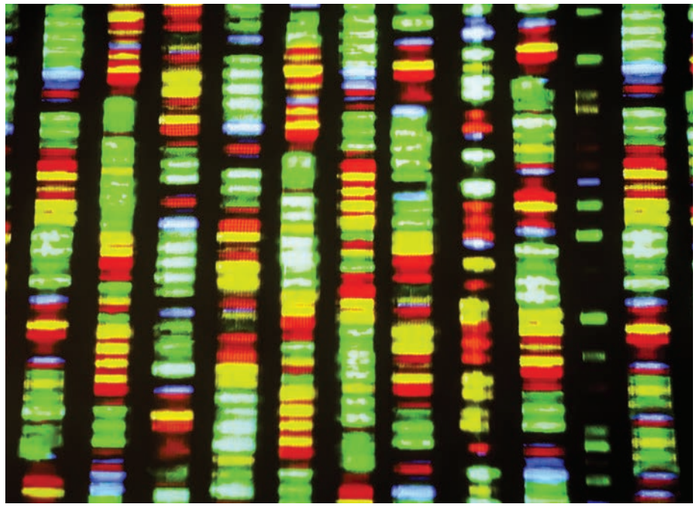
FINDINGS FROM ROGEL researchers published in *Cancer Discovery*, show how a specific nucleotide metabolite, called GTP, controls responses to radiation and chemotherapy in an unexpected way.

“We learned that if you increase a cell’s GTP levels, it makes it really resistant to radiation or chemotherapy. Lowering GTP levels, the cell becomes much more sensitive,” says **Daniel Wahl, M.D., Ph.D**.

Researchers have long known that levels of nucleotides like GTP control how fast DNA damage is repaired, which in turn controls sensitivity to therapies.

Researchers previously thought that this only happened because nucleotides are the building blocks that form DNA. But these findings uncover an entirely new way that nucleotides control DNA repair.

“Instead of only affecting the physical structure of the DNA, it also acts as a signaler. The levels of GTP turn on a signaling pathway and give cells instructions to repair damaged DNA,” says Wahl.



IMPROVEMENTS IN HUMAN GENOME DATABASES OFFER A PROMISING FUTURE FOR CANCER RESEARCH

A GENE SEQUENCING METHOD called ribosome profiling has expanded our understanding of the human genome by identifying previously unknown protein coding regions. Also known as Ribo-seq, this method allows researchers to get a high-resolution snapshot of protein production in cells.

Ribo-seq has the potential to advance cancer research, but many of the discoveries enabled by Ribo-seq provide an untraditional view of where and how protein production might happen.

As such, scientists must first verify these regions code for proteins.

“Ribo-seq has garnered major interest for use in studying protein production in cancer cells to identify specific abnormal proteins as targets for immunotherapy or other treatment approaches,” says **John Prensner, M.D., Ph.D**. The study is published in *Molecular & Cellular Proteomics*.

WHY DON’T MORE PEOPLE GET GENETIC TESTING FOR CANCER?

NOT ENOUGH PEOPLE are getting genetic testing for cancer, according to recent research.

Germline genetic testing, in which inherited DNA is sequenced, is recommended for patients diagnosed with cancer to enable genetically targeted treatment and identify additional relatives who can benefit from personalized cancer screening and prevention. Guidelines recommend this testing for people with cancers including breast, ovarian, pancreatic, colorectal, prostate and others.

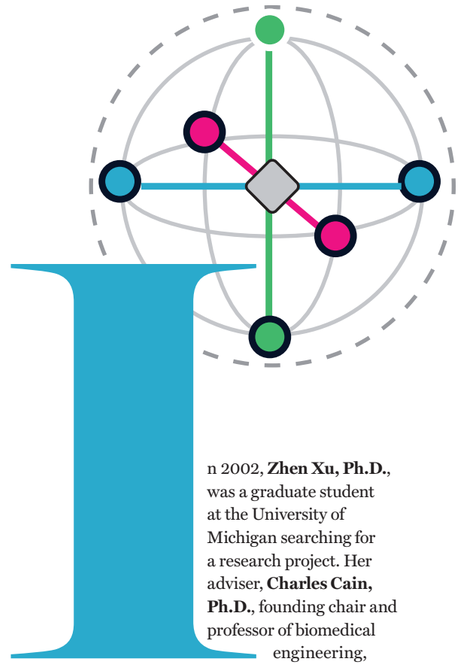
Despite the knowledge this could bring to patients and their relatives, researchers found that only 6.8% out of a million patients underwent the testing within two years of receiving a diagnosis. The testing rates were lowest among Black, Hispanic and Asian patients.

“We were surprised at the low rates of testing given the growing evidence for the benefits of results for patients and their families,” says **Steven Katz, M.D., M.P.H.**

Making the Impossible Possible

A surprising discovery in graduate school led U-M biomedical engineer Zhen Xu to the first non-invasive, non-thermal tumor resection technique using ultrasound. Twenty years later, she and a team of Rogel researchers have received FDA approval to treat patients with liver cancer.
Here's how they did it.

By Anna Megdell
Photos by Erica Reist Bass



In 2002, **Zhen Xu, Ph.D.**, was a graduate student at the University of Michigan searching for a research project. Her adviser, **Charles Cain, Ph.D.**, founding chair and professor of biomedical engineering, was approached by a pediatric cardiologist, **Achi Ludomirsky M.D.**, who asked Cain and Xu if they could develop an approach to treat children with congenital heart disease by resecting heart tissue without cutting open the patient to put further strain on already sick kids. The procedure needed to be non-invasive and non-toxic. After months of research, nothing had worked.

"Cain told me that I couldn't rely on preexisting research or literature. I was trying to make something completely new. He said I needed to think 'out-of-the-box,'" says Xu, now a professor of biomedical engineering at the U-M College of Engineering. "His exact words were, 'I don't want your innovative mind to be contaminated by conventional wisdom.' I thought 'that's great, but how!?'"

> **"We needed to understand the precise mechanism on how cavitation was generated and controlled so we could tell the scientific community why, in the past five decades, nobody was able to generate and control cavitation to treat patients, but now we could."**
>
> Zhen Xu, Ph.D., left

Xu began investigating how ultrasounds generate cavitation, a process that creates micro-bubbles in tissue that expand and collapse, eventually erasing the tissue. Ultrasound was known to be non-toxic and non-invasive; babies underwent imaging all the time at no harm to them, so Xu figured it could be effective. "But at the time, nobody thought cavitation could be controlled to actually target and remove specific tissue," she explains.

For months, Xu explored new ways to manipulate ultrasounds to no avail. Even though ultrasound is above human hearing range, ultrasound bursts to generate cavitation are typically pulsed at a frequency that humans can hear, including her lab mates. "They said my experiment was too loud," Xu says, laughing. Then one day, using pig hearts, Xu tested how tissue responded when submerged in water and exposed to pulsing sound waves at a very powerful amplitude, but with very short bursts of microsecond length and pulsed at a frequency beyond the human hearing range.

"It only took a few seconds," she says. "I saw something that looked like smoke rising out of the water. But it turns out it wasn't smoke. It was tiny, tiny debris from the tissue.

"In one minute, I saw a hole in the pig heart tissue," Xu continues. "My first reaction was, 'Am I dreaming?'"

Science Behind the Serendipity

This breakthrough led Xu down a decades-long path to developing what is now known as histotripsy, a completely non-invasive—no needles, no incision, no exposure to radiation, non-thermal—way to destroy the target tissue.

Instead of traditional methods, histotripsy functions mechanically. Ultrasound waves are pinpointed inside the target tissue or a tumor to generate a cluster of microbubbles from the pre-existing nano-meter gas pockets. Microbubbles contract and expand repeatedly adjacent to cells, producing high local mechanical strain on the cells. Eventually, the cell walls get destroyed. Because it's mechanical, the cell death is irreversible.

But before histotripsy was fully understood, Xu needed to make sure the hole she saw in the tissue wasn't a fluke. She repeated the process three times, in different locations, and each time, a hole emerged. "Then I could finally let myself admit that what I saw was true," Xu says. She showed her results to Cain. "We realized we had something special on our hands. This was the beginning of our journey."

From there, Xu and a team began to study which parameters led to the hole in the tissue. She knew she could target and destroy tissue using ultrasound; now she needed to understand how it happened. "I was able to recreate it in terms of engineering," Xu explains. "But it wasn't clear why those specific parameters had worked. We needed to understand the precise mechanism on how cavitation was generated and controlled so we could tell the scientific community why, in the past five decades, nobody was able to generate and control cavitation to treat patients, but now we could."

Xu admits that the first discovery, the very first hole in the tissue, was serendipity. "I tried some parameters that were totally different from anything I tried before, and it worked out." From there came the hard work, and

20 YEARS OF RESEARCH ↬

2002 Xu first began researching how to kill tumor cells non-invasively ↬

many years, of scientific exploration to turn the initial discovery into a real technology that could eventually be used on patients.

For a decade, through graduate school and into her post-doctoral and early career years, Xu and team members studied the mechanisms behind histotripsy and developed the equipment needed to make results consistent. "Our job is to make the impossible possible," she says. "I find inspiration when it looks like things can't be accomplished. It makes me want to look closer."

Once Xu and her team established the mechanics underlying histotripsy, she reached out to **Mishal Mendiratta-Lala, M.D.**, and **Clifford Cho, M.D.**, at Michigan Medicine to begin exploring if this new technology could be used clinically to help patients with tumors.

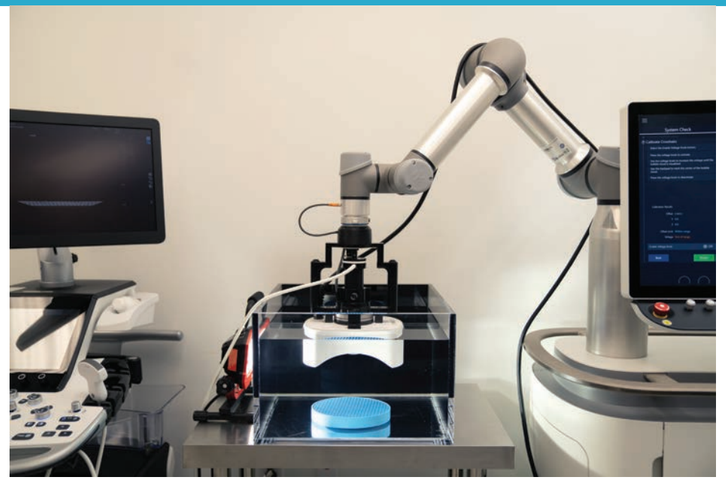
Building the Team

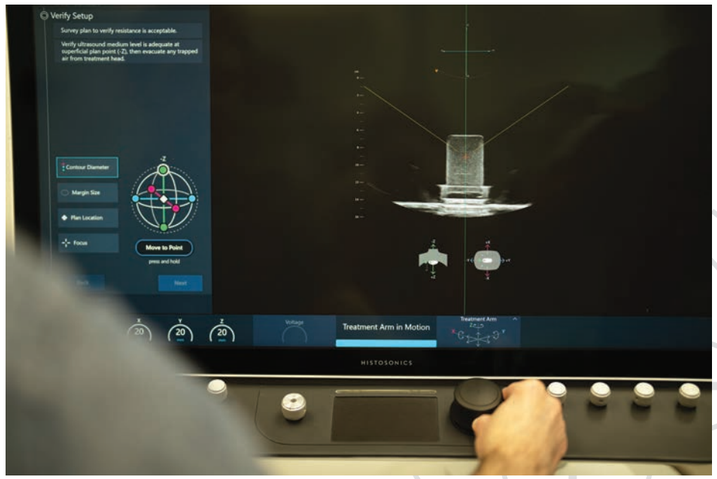
In 2017, Mendiratta-Lala, professor of radiology, heard about a researcher in biomedical engineering who was looking for someone to help interpret liver images on animals. "Right away, I was very interested in getting involved," she says. That researcher was Xu. Together, they started a preclinical project to see if histotripsy worked on liver tumors in animal models.

Xu also reached out to Cho, professor of surgery, who runs a lab that studies cancer immunotherapy. "We did a bunch of experiments that showed histotripsy could be used as a platform for cancer immunotherapy."

These projects led to more research, which led to collaborating with researchers from the University of Wisconsin. This preclinical worked helped establish a clinical trial to test histotripsy on human patients who have either primary or metastatic liver cancer in the United States and Europe.

The trial's run-of-show is straightforward. Patients get an MRI within 30 days of enrollment and standard blood and liver tests the week of the procedure. On the day of the procedure, they go under general anesthesia to control their breathing. Radiologists perform the histotripsy procedure in the interventional radiology procedure room. They get an immediate post-procedure imaging study to confirm that the tumor was completely





The histotripsy device, Edison™, was created by HistoSonics, a startup company that licensed Xu and her team's histotripsy patents from U-M.

treated. After the procedure, the patient stays in recovery until the anesthesia wears off. Patients then can go home that same day, returning for imaging a month later to make sure there is no disease recurrence.

The results of the clinical trial showed histotripsy was safe and effective in destroying liver tumors and led to complete tumor regression.

But the clinical trial results also revealed another effect: Not only did histotripsy destroy the targeted area of the organ, but it triggered the body's immune system as well. Cho explains that common cancer treatments don't often effectively incite an anti-tumor immune response. Many tumor ablation techniques rely on methods like heating or freezing the tumor, which prevents the immune system's ability to see and recognize the tumor. But histotripsy's mechanical nature changes the game.

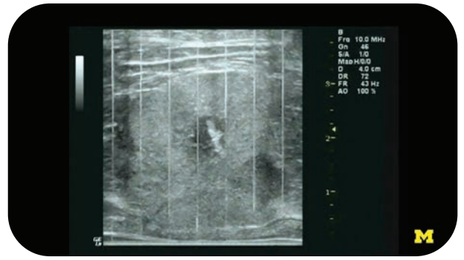
"A lot of our preliminary studies demonstrated, in various forms in many kinds of cancers, that whenever we ablated the tumors using histotripsy in mice, we saw very measurable immune responses generated against that tumor," Cho explains. "For example, if there were two tumors in mice and we used histotripsy on just one, we saw an anti-tumor immune response against the other tumor."

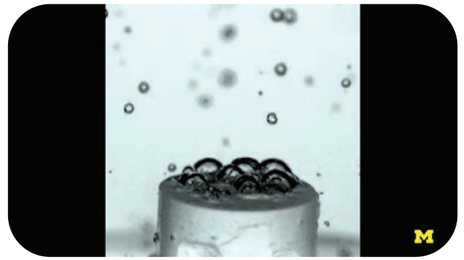
"We noticed that if we treat with histotripsy, the whole tumor as well as tumors elsewhere in that animal were going away a few weeks later," Mendiratta-Lala adds. "We're seeing this immune system activation and we're priming the body to fight tumor elsewhere. Triggering the immune system could lead to things like addressing distant metastasis or making immunotherapies more potent. If this really is going to happen in patients, it will obviously be life changing."

Now, the team is interested in understanding why. They are conducting another clinical trial combining histotripsy and immunotherapy. "We still need to see how the immune response works in human patients," says Mendiratta-Lala. Early data from the clinical trial in Spain showed that untreated tumors shrink concurrently with tumors that have received treatment.

In addition to destroying the tumor, results show that histotripsy changes the tumor microenvironment,

What is Histotripsy?





Histotripsy is the first noninvasive, non-ionizing and non-thermal ablation technology guided by real-time imaging. Using focused ultrasound delivered from outside the body, histotripsy mechanically destroys tissue through cavitation, rendering the target into acellular debris.

Scan to see a video of histotripsy in action.

2002 Xu first discovered cavitation in pig heart tissue using non-invasive, non-thermal ultrasound

2012 Xu and her team spent 10 years investigating the mechanism and physics behind histotripsy

2016 Histotripsy clinical trial in humans began in patients with benign prostatic hyperplasia

altering its blood oxygen content. "It convinces tumor cells not just to die but to die in specific pathways that are almost perfect for generating immune response," Cho explains. "We found that it actually reprogrammed immune cells to acquire certain abilities to kill tumor cells that they didn't have before."

For Cho, this leg of the research—investigating histotripsy's unexpected effects on the immune system—embodies what it means to follow the science.

"These immune effects have led us to more interesting and nuanced areas of study than we ever could have anticipated." he says.

Patients First

In addition to the clinical trial's staggering results, the clinicians on the team emphasize what it means for patients to have a treatment that is successful and completely non-invasive.

"As someone who does interventional procedures, recovery from histotripsy versus other forms of treatment is incredible," says Mendiratta-Lala. "Usually after an ablation procedure that uses microwave or radiofrequency, patients can have tenderness and a little bit of pain; they can't move for five hours after the procedure." But with histotripsy, the only recovery is from the general anesthesia. "Many patients ask if the procedure was even done because they don't feel any pain," Mendiratta-Lala continues. "They can just get up and walk out the door when they're done."

Valerie Khaykin is the clinical trial coordinator of the histotripsy trial. She recruited patients to the trial and guided them through the process. U-M was the highest enrolling institution with 10 patients to date thanks to Khaykin's efforts. She says the most surprising part of the trial for the patients lies in the consults. "Patients and sometimes even nurses and the medical professionals can't believe there's no recovery aside from the anesthesia," she says. "We've gotten really good at explaining how the technology works."

Khaykin says that histotripsy is especially comforting for patients who might not qualify for typical treatments. "For people in their 80s or for those who have comorbidities, not having to undergo traditional surgery to remove their tumors is a gamechanger."

Strict guidelines are put in place on who can qualify for the clinical trial. While necessary to prove the effectiveness of histotripsy and to establish a level baseline, the qualifications can exclude patients whose labs are just outside the established range of candidacy but who might still benefit from treatment. For Khaykin, these are the patients who stay with her, and who come to mind when thinking about how FDA approval will impact many patients with cancer.

"With FDA approval, we now won't have to worry about those technicalities," she says. "For some patients, histotripsy is curative. But even if it's not, it has the potential to activate their immune system or ease disease burden. It's a relatively benign treatment and doesn't discriminate in terms of age or disease progression. We've treated so many people with different pathologies, different overall health. It has the potential to be a great, universal option. It's giving patients a lot of hope."

"We noticed that if we treat with histotripsy, the whole tumor as well as tumors elsewhere in that animal were going away a few weeks later," Mishal Mendiratta-Lala, M.D., says.

To FDA and Beyond

HistoSonics, a startup company, licensed Xu and her team's histotripsy patents from U-M and created the clinical histotripsy device (Edison). HistoSonics received FDA approval in October 2023 for the Edison platform to treat patients liver disease using histotripsy. Though the culmination of 20 years of work, Xu is eager for the next step. "We're aiming for FDA approval on renal tumors and pancreatic tumors. And there's the combination trial between histotripsy and immunotherapy. We now have this technology that hopefully will be used for many, many things," she says.

Xu receives emails from patients around the world, wanting to know if histotripsy could be used to help treat their disease. "I've been working on this for over 20 years, and there are so many people involved who have been working so hard," she continues.

"Now we're at the point where we can really see that it's going to benefit patients. There are so many people who need help. It's not time to stop. We have more work to do." ⊠

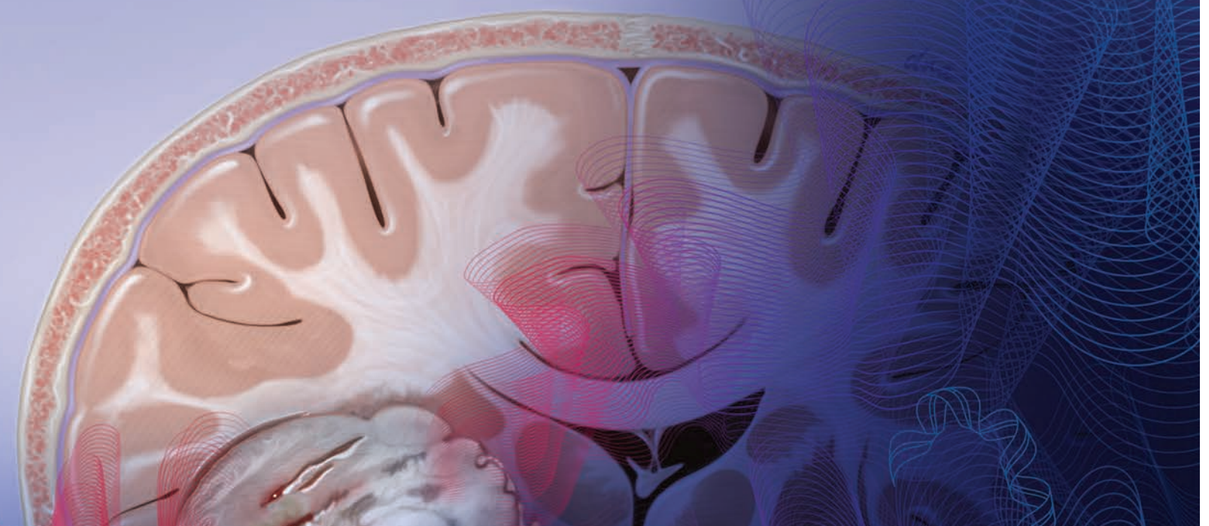
Disclosure:
U-M retains a financial interest in HistoSonics, as do a number of researchers who were involved in this project and who helped develop the technology licensed to HistoSonics, including Xu, who is a company co-founder, stockholder and consultant, and Cho, who is a consultant. Each stands to benefit financially from the success of the platform.

2019 Histotripsy clinical trial in patients with liver tumors began ➔

2022 HistoSonics applied for FDA approval for histotripsy treatment of liver tumors ➔

2023 HistoSonics received FDA approval for liver tumor treatment in humans

A Path of Hope



While brain cancers are not always lethal, the most common form, glioblastoma, is aggressive and incurable, with a median survival of one and a half years. A team of researchers, foundations and families have pushed Rogel to the forefront as a hub for cutting-edge brain cancer research.

By Rebecca Dzombak

Illustration by Alex Webber

The Rogel Cancer Center has been home to leaders developing groundbreaking research and advancing knowledge on brain cancer for nearly four decades. But in the last decade, U-M has evolved to become a world-renowned institution for treating aggressive brain tumors. From identifying deadly tumors sooner, understanding the biology of how and why they grow, and uncovering promising new treatments, Rogel researchers are carving a path that creates hope for patients, becoming a hub of innovation in the process.

A Two-Pronged Attack For High-Grade Gliomas

Maria Castro, Ph.D., and **Pedro Lowenstein, M.D., Ph.D.**, are pioneers in tackling aggressive brain tumors. They specialize in gene therapy-mediated immunotherapy for high-grade gliomas and collaborate with researchers across U-M to translate their therapies for adult and pediatric patients. Their work, more than two decades in the making, is about to pay off.

"Gliomas are very aggressive, and it's important to make progress, but that progress can be terribly slow," says Castro, R.C. Schneider Professor of Neurosurgery, professor of cell and developmental biology and co-director of the Biosciences Initiative in Brain Cancer Technologies. "There's been a lot of progress in identifying gliomas, imaging them and running diagnostics, but this has had little impact on therapeutic outcomes."

When Castro first began working with Lowenstein on brain tumors in the 1990s, gene therapy was a new, emerging field, and their team was at the frontier's edge, focused on treating high-grade gliomas.

"No one was doing gene therapy," Castro says. "It was a very new technology." Single-vector approaches were effective for killing rapidly dividing cancer cells, but sparking an immune response in the brain was challenging. Lowenstein, Richard C. Schneider Collegiate professor of neurosurgery, professor of cell and developmental biology and professor of biomedical engineering, discovered that the brain's immune system lacks dendritic cells, which are crucial for initiating immune responses. That lack could explain the difficulty in eliciting effective anti-glioma immune responses.

Pedro Lowenstein, M.D., Ph.D., and Maria Castro, Ph.D., in their lab

Photo: Michigan Photography

To trigger a natural immune response in the tumor cavity after resection, Castro and Lowenstein wanted to use a new two-vector approach: "One gene kills the tumor cells, the other activates the immune system," Castro says. "It's a two-pronged attack."

Castro, Lowenstein and their team built two adenoviral vectors to be injected into the brain cavity post-resection. The first vector delivers the HSV1-TK enzyme, which when administered with valacyclovir gives rise to a toxic compound. The compound kills glioma cells and triggers the release of tumor antigens into the tumor microenvironment. The second vector delivers FMS-like tyrosine kinase 3 ligand (Flt3L), which recruits dendritic cells into the tumor microenvironment. The dendritic cells detect tumor antigens, travel back to the lymph nodes with their message to activate the T cells, which then attack the remaining tumor cells.

The early results were surprisingly promising, Castro and Lowenstein recall.

"When you use each therapy independently, neither one works so well," Castro says. "But when you combine them, the efficacy just rises through the roof."

The therapy also worked particularly well for model animals with gliomas that carried the IDH1 mutation, which Castro describes as "a death sentence delayed in time." Mutant-IDH1 tumors always come back and are resistant to radiation treatments. But patients with mIDH1 tumors tend to have longer survival times—in part, as Castro recently published in *Science Advances*, because the mIDH1 tumor microenvironment is epigenetically modified such that the immunosuppressive cells have lost their immune suppressive capacity. Castro and Lowenstein's dual-vector approach takes advantage of that mutation.

In early studies, they found 98% of animals with mIDH1 glioblastomas were cured, a finding "never seen before in any tumor type," Castro says. "It worked beautifully."

Castro and Lowenstein moved to Michigan Medicine in 2011 and began the study of the dual-vector treatment, targeting high-grade glioma patients with wild type IDH1 in 2013 with support from the Phase One Foundation. The results, recently published in *The Lancet Oncology*, from 18 patients treated as part of a Phase I trial were stunning.

Patients in the study saw median survival times of about 21 months, a significant gain from the historic survival of 14.6 months. The two-year survival rate was nearly 40%; seven patients survived beyond two years, three survived beyond three years, and one was still alive 60 months after initial study enrollment.

Pediatric oncologist Andrea Franson, M.D., works with Castro and Lowenstein to bring treatment options to children with cancer.

Photo: Leisa Thompson

"We believe this gene therapy approach may be even more powerful in patients with the IDH1 mutation," Castro says. "I predict it will be really effective in that patient population, so that's one of the future trials we're working on now."

Part of the promise of the treatment is the potential for long-term therapy. Castro and Lowenstein found that HSV1-TK persisted in patients' brains for more than two years. Currently, valacyclovir is only authorized to be administered for a total period of four weeks, so their findings suggest that if the administration of valacyclovir could be extended to months or years, patient survival times could be extended proportionally.

"This was totally unexpected," Lowenstein says of HSV1-TK's longevity. "It gets me particularly excited, it's very promising. It certainly justifies going into larger trials."

Lowenstein and Castro are now developing a phase Ib/II trial for the dual-vector approach for wild type and mIDH1 glioma patients. Overall, they hope their work will help the field and that the FDA will have broader acceptance of multi-pronged treatments like theirs.

"The way to push this forward is in combination," Castro says.

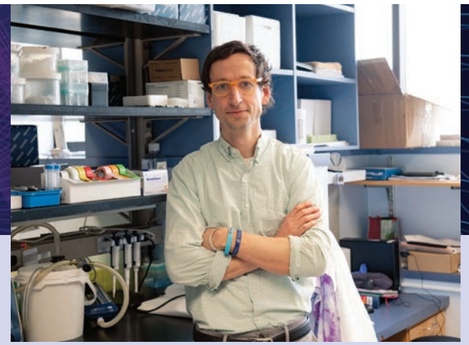
Not Only One Diagnosis

Pediatric oncologist **Andrea Franson, M.D.**, works with Castro and Lowenstein to bring their groundbreaking dual-vector treatment to pediatric patients. Franson's focus has been on high-grade gliomas with the H3G34R mutation, which is present in a subset of patients with pediatric high-grade glioma. This effort is supported by Ian's Friends Foundation.

Typically, these patients live only 12 to 24 months from diagnosis.

"In so many of these tumor types, the need for better treatments and outcomes is so desperately high," Franson says. "We're dealing with these really rare tumors, so thankfully the numbers of patients are low, but there are still a lot of tumors and a lot of need."

Like mIDH1 tumors, pediatric H3G34R mutant tumors have incapacitated immunosuppressive cells, making them potentially susceptible to the dual-vector treatment. Franson, assistant professor of pediatrics, is working under the mentorship of Castro and Lowenstein to explore anti-tumor immune responses in H3G34-mutated versus non-mutated tumors in mice, probing the system for points that could be exploited



"We're going to be here until we find a cure"

From 2014 to 2015, **Carl Koschmann, M.D.**, treated Chad Carr, a 4-year-old boy diagnosed with DIPG. When Chad passed away, the relationship that had formed between the Carr family and Michigan Medicine led to Chad's mother, Tammi Carr, forming the ChadTough Foundation, which supports pediatric patients and their families and funds national research on DIPG and other aggressive, high-grade gliomas.

"When Chad was diagnosed, Michigan hadn't focused much on DIPG," Carr says. "We wanted to do something to improve that, because that's Michigan, that's family."

In under a decade, the ChadTough Foundation and its donors have helped Michigan become an international leader in pediatric brain cancer treatment and research, including the foundation of the Chad Carr Pediatric Brain Tumor Center in 2016.

"In such a short period of time, U-M is now without a doubt one of the top centers in the world when it comes to DIPG," Carr says. "Michigan has said, 'We need to be better. We need to do better.'"

In 2020, ChadTough joined with the Michael Mosier Defeat DIPG Foundation, created in 2015 after Michael passed away from DIPG. Together, the ChadTough Defeat DIPG Foundation has partnered with more than 40 families around the country to spread awareness, supporting patients and their families and funding critical research.

"Ultimately, we're not where we want to be, but progress is being made, and life expectancy is basically increasing. There are more trials now than ever," Carr says. "We want every family to feel like their child is honored and remembered and making an impact on the disease. We're going to be here until we find a cure."

ChadTough™
Defeat DIPG Foundation

to trigger an immune attack using the dual-vector treatment.

Translating Castro and Lowenstein's genetic immunotherapy approach for pediatric patients is critical, in part because so many tried and true treatments have fallen short.

"Chemotherapy, radiation therapy and surgery may work for the short term, but the tumors don't stay away," Franson says. "People have tried many, many things over the last several decades, but for the toughest tumors, there's really been no progress."

Part of the delay in successfully treating H3G34R high-grade gliomas lies in researchers' lack of knowledge about their fundamental biology. Scientific understanding of brain tumors' genetics (including histone mutations like H3G34R) didn't come about until recent years.

"The more we dig into tumor genetics, genomics and proteomics, the more we realize there are all these subcategories of tumors," Franson says. "We may be giving patients the 'same' diagnosis, but really, it's not."

Franson hopes to hone treatment by improving tumor profiling at the diagnostic state. While that reality may be distant, methylation profiling is a promising step down that pathway and may lead to different treatments choices made from the time of diagnosis. Franson is a co-lead investigator for a national phase I clinical trial that's using genetic tumor profiling to optimize drug treatment.

"If we understand enough about how these tumors form and progress, we'll get closer to finding what actually helps patients," Franson says.

Pediatric oncologist **Carl Koschmann, M.D.**, who serves as co-director of the Chad Carr Pediatric Brain Tumor Center, is developing a promising treatment for pediatric patients with diffuse midline gliomas (DMG) with the H3K27M mutation. The median survival time for patients with these high-grade gliomas is around 12 months, even with radiation therapy, "so there's a lot of progress to be made," Koschmann says. "Currently, we can't remove them. We can barely biopsy them."

Koschmann's dual life in the clinic and the lab, including starting his own lab in 2016 after training with Castro and Lowenstein, has enabled him to work on the cutting edge of both understanding and treating tumors with this mutation. His most recent advancement builds on studies of ONC201, a dopamine receptor antagonist, that has been explored for use in diffuse midline glioma patients. In an early study, ONC201 was found to be safe and cross the blood-brain barrier, but it was not effective at treating adult glioblastoma. But several younger patients in that trial who had DMG that harbored a hallmark H3K27M mutation showed a potential response, opening the door to further study.

A phase I trial of ONC201 opened in 2017 to examine the H3K27M mutation and its tie to better survival times. U-M was one of a few early trial sites. During this time, Koschmann worked with **Sriram Venneti, M.D., Ph.D.**, co-director of the Chad Carr Pediatric Brain Tumor Center, to understand why the drug might be more effective in cells with the H3K27M mutation. Their studies of spinal fluid from patients treated at U-M led to the discovery that ONC201 disrupts mitochondrial behavior and changes the tumor's epigenetics, "essentially restoring tumor cells to be a lot more like normal brain cells after treatment," Koschmann says.

Their study, recently published in *Cancer Discovery*, shows that in a cohort of 36 DMG patients treated after initial radiation, the median survival time was nearly 22 months. This therapy is the first single therapy to improve outcomes for these patients, and a phase III trial is underway.

"Since 2017, we've treated more than 100 patients with this therapy here at U-M," Koschmann says. "Their overall survival is noticeably better than historical survival, so it's exciting to see that there is a crack in the armor. I'm optimistic that in our generation of experimental treatments, we'll have patients surviving five or 10 years, or beyond. That's where the future is heading."

Catch Tumors Early, Treat Them Right

Because treatments for these brain cancers still offer relatively little to patients, catching the disease early—and maybe even predicting patients' risks of developing them—is critical.

"Part of what makes these cancers so lethal and so hard to treat is a lack of early diagnostics," Castro says. "Think about skin cancer, where a lot of progress has been made. They recommend you do skin scrutiny once a year, and if you see something that looks suspicious, they immediately take it out. But with brain tumors, they're silent killers. By the time the patient comes to the doctor, the tumor is already very advanced."

Radiation oncologist **Michelle Kim, M.D.**, is working to change that. As professor of radiation oncology and co-chair of the Rogel Cancer Center neuro-oncology clinical research team, she's developing more accurate, precise imaging to characterize and predict tumor growth early to inform individualized, targeted treatment.

Collaborating with **Yue Cao, Ph.D.**, professor and head of functional imaging, Department of Radiation Oncology, Kim has worked to understand the imaging phenotypes characterizing the biologic features of glioblastomas and brain metastases. Most recently, Kim focuses on using perfusion and diffusion-weighted multiparametric MRI to identify hyperfused and hypercellular regions in newly diagnosed, therapy-resistant glioblastomas. The approach identifies regions that remain after resection and are missed by standard imaging technologies. Targeting these regions of treatment resistance using dose-escalated radiation therapy, a cohort of adult patients had favorable survival outcomes in a phase II trial led by Kim and her collaborators.

"The initial outcomes from this study appear to be promising," Kim says, and the work is being developed into a national phase II/III randomized trial through the National Clinical Trials Network. To support this effort, Kim received the inaugural NIH/NCI R50 Research Specialist (Clinician Scientist) Award in early 2023. She is developing this study through the Alliance for Clinical Trials and NRG Oncology, which could be the first fully collaborative cooperative study between two major oncology groups in the United States.

"We are very excited about this potential opportunity to pioneer a new direction in the use and implementation of integral imaging biomarkers to improve outcomes in patients with malignant brain tumors," Kim says.

Radiation oncologist Michelle Kim, M.D., works to develop imaging to predict tumor growth early, leading to individualized, targeted treatment.

Photo: Leisa Thompson

The Future Of Brain Cancer At Rogel

The need and the momentum for rapid, radical change in the field is clear to all these researchers, whether it's detecting tumors sooner, throwing new combinations of treatments at the disease or building a national registry of brain cancers.

Despite the tough uphill battle, Rogel researchers remain dedicated and hopeful.

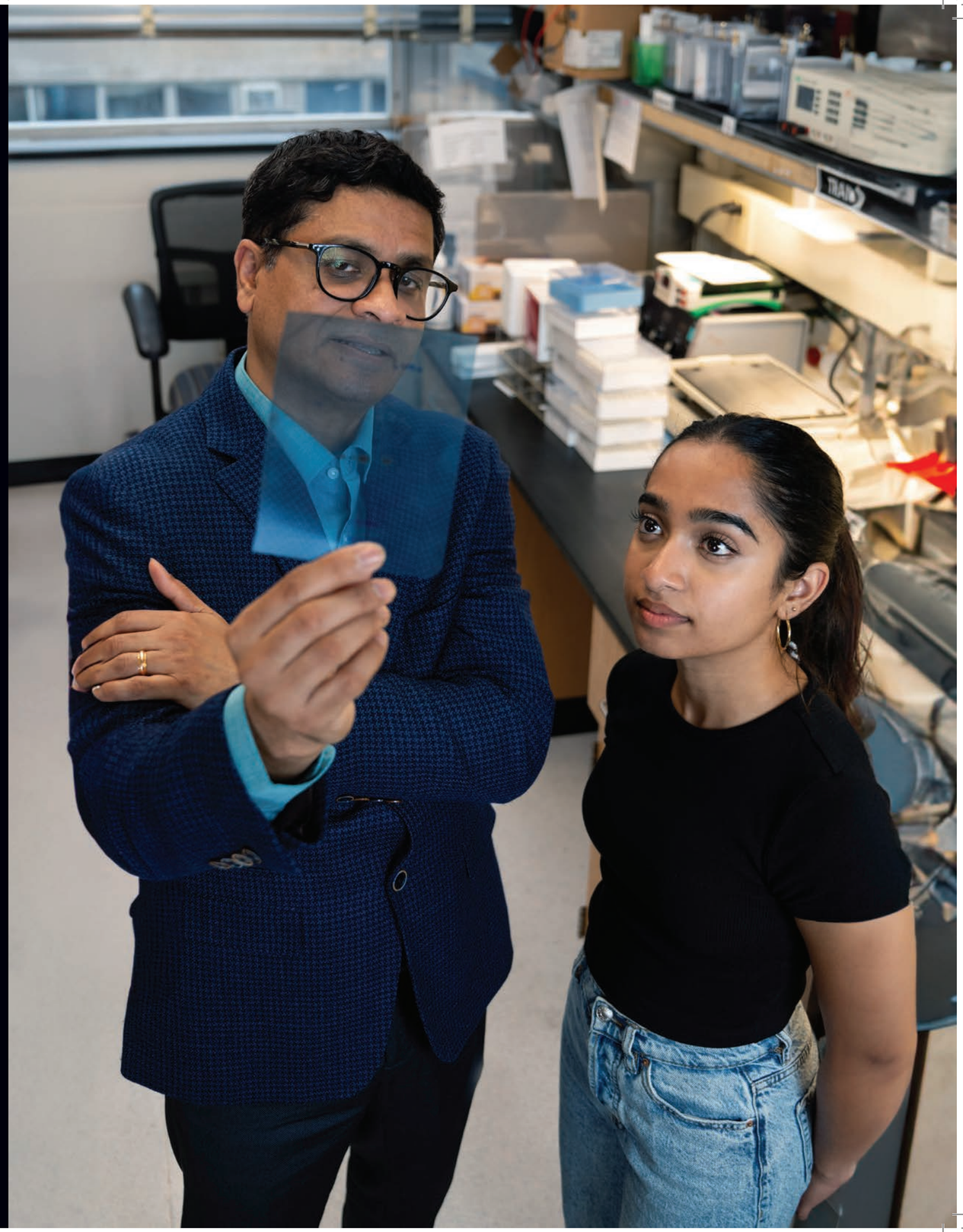
"At U-M and in the field of neuro-oncology, we recognize the importance of multidisciplinary collaboration," Kim says. "There's not just one person who's going to find the silver bullet. Collective creativity and thinking from different angles are critical for improving patient outcomes. And that's the approach and the legacy we have here at U-M."

"We need to work together, combine our efforts to attack this monster from several angles," Castro adds. "Once we're able to combine multiple approaches—immunotherapy, radiation, chemotherapy, targeted gene therapies—we'll be able to make a dent in this disease. This is what we believe quite strongly."

Training Tomorrow's Cancer Leaders

Rogel's summer training programs expose students early on to cancer career options, hoping to foster a passion for the field and lifelong connections.

By Nicole Fawcett
Photos by Erica Reist Bass and Leisa Thompson



Navya Valavala shows her mentor, **Dipankar Ray, Ph.D.**, a Western blot from her latest experiment.

"A lot of cell death is happening here," Ray points out. "The question is why?"

He offers some ideas of what Valavala can do next.

"Watching him troubleshoot the experiment, you see the gears shifting in his head as it happens," she says. "Dr. Ray makes connections very fast. Just being around him is so inspiring."

Valavala, a junior biology major at Emory University, spent the summer working with Ray as part of the Rogel Cancer Center's Cancer Research Summer Internship Program, known as CaRSIP. It's a longstanding program that Ray took over in 2018. And it's one of a half dozen summer training programs Rogel offers to encourage and promote students to take an interest in cancer careers.

Over the summer, these programs bring students in high school, college and medical school to the University of Michigan to get a glimpse of life as a cancer researcher or provider. While each program has a slightly different focus, the underlying goals overlap: expose students to cancer careers to learn the many ways they can get involved.

"Over the last decade, we've seen so many advances in cancer treatments that are extending lives," says Sarah **T. Hawley, Ph.D., M.P.H.**, Rogel's associate director for training, education and career development, or TrEC. "But we need people to keep going into the cancer field to continue that mission of reducing the burden of cancer."

Broadening Awareness Of Cancer Careers

Organized under the TrEC umbrella, the programs start with high school students to introduce them early on to career options they may not know about.

"Most students only know about medical school or a professional school like physical therapy. Or maybe forensic science because it's so common on television. If you like science those are the defaults. They don't know research is an option," says **Megan Radyk, Ph.D.**, a post-doctoral fellow at Rogel.

In 2022, Radyk started BioMed Focus, an eight-week summer research program for high school students. In its first year, the program had three students from Lincoln High School in Ypsilanti. The next year, they increased to nine students, adding Belleville High School.

The program packs a heavy load. Students start off learning research basics, such as how to use a pipette and techniques like gel electrophoresis. Then they spend 40 hours a week in a lab, working with a mentor to pursue their own research project. Some topics were neural function under stress, iron levels in pancreatic cancer and RNA binding proteins in breast cancer.

"You can get interested and energized by taking science classes," says **Yatrik Shah, Ph.D.**, Horace W. Davenport Collegiate Professor of Physiology, who helps oversee BioMed Focus. "But there's something different when you come into the lab, extract DNA and then see it in the tube. It has a different spark. Students who are exposed to that early can see exactly how science is done in the laboratory. That has a different impact than just didactic classes."

Even as students progress through their education, cancer careers aren't always a clear option. **Lori Pierce, M.D.**, says she "just happened to find" radiation oncology as a career when she was in medical school. Now, she wants to give medical students more exposure to all cancer disciplines.

"There are no planned rotations in many areas of oncology. We want them to see the richness of the profession early in their medical careers," says Pierce, professor of radiation oncology.

When Pierce was president of the American Society of Clinical Oncology, she partnered with **Jamie Von Roenn, M.D.**, ASCO's vice president of education, science and professional development, to create the four-week Oncology Summer Internship program. Run through ASCO, medical schools like the University of Michigan apply to participate.

Through the Oncology Summer Internship, second-year medical students spend four days a week shadowing physicians in different settings—medical oncology, radiation oncology, surgical oncology, pathology, radiology, physical medicine, gynecological oncology, otolaryngology, among others.

"We need to increase the number of people who are going into cancer-related fields across the board," says **N. Lynn Henry, M.D.**, professor and interim division chief of hematology/oncology, who, along with Pierce, helped bring the program to U-M. "With physician shortages anticipated in the coming years, we need to give early career medical students broad exposure to all cancer-related fields."

Across all the summer programs, students at every level repeatedly comment on how it's exposed them to new ideas and opportunities.

"After about the fifth day, I saw there was honor in many different careers in oncology," says **Antasia Copeland**, who participated in the Pathways Undergraduate Fellowship, a program for college students in Michigan. Copeland is finishing a bachelor's degree in biology at the University of Michigan-Flint, with plans to apply to medical school.

"I know I want to be around patients all day and be hands-on with treatment. But I realize I don't necessarily have to be an oncologist. I could be a geneticist or a genetic counselor," she says. "It was awesome to hear the different trajectories everyone took."

Fostering Diversity

Running through each program is a focus on fostering diversity, equity and inclusion, including by recruiting students from backgrounds underrepresented in medicine to participate. Several programs require applicants to submit a statement highlighting anything in their background, interest or experience that shows their commitment to or awareness of issues of inequity in education and health care. Some programs specifically work with students from schools that do not have strong science curricula. Some programs focus on engaging students from Rogel's catchment area, which is the state of Michigan, while others have a national focus.

"If we want to make the research community more diverse, we have to act on it by bringing people up and showing them how they can get into the system. Sometimes all someone needs is that push," says **Erez Cohen, Ph.D.**, a post-doctoral fellow in cell and development biology and an instructor for Developing Future Biologists.

Pathways students came to Ann Arbor for the program's final day and toured research labs. "I saw there was honor in many different careers in oncology," says Antasia Copeland, pictured at far left.

Pathways students heard from Rogel faculty and staff about multiple options to pursue careers in cancer research and care.

Developing Future Biologists is entirely run by post-doctoral and graduate students at U-M. In 2023, they brought in 32 students from schools across North America. Students spend a very intense week on site at U-M labs conducting research. The program looks for undergraduate students at smaller schools who may not otherwise be able to connect with a world-class cancer center.

Similarly, the Pathways Fellowship boosts undergraduate students from any Michigan university, excluding U-M's Ann Arbor campus, with an aim of promoting interest in cancer careers, both research and clinical, among students from Rogel's catchment area.

"One goal is to get more students from across the state to have access to the breadth of research and care that happens at U-M and the Rogel Cancer Center. Some of the students who come to this program don't know all the options available to them or how to hone their interests in science or medicine into a career, especially a cancer-related career," Hawley says.

Recruitment outreach for Pathways focuses on students with backgrounds traditionally underrepresented in medicine and science, including students from schools across the state that don't have strong research programs or access to a comprehensive cancer center. The goal is to benefit the students while also fostering more representation, broadly defined, in the cancer field. Students who have participated in the program have gone on to graduate programs in cancer biology and to medical school.

CaRSIP, on the other hand, looks to foster diversity among top-tier science students. Every year, more than 180 students from across the country apply for 10-12 spots. Requirements are very stringent: GPA above 3.0, prior research experience, two recommendations and a serious interest in cancer research. Weight is given to students' diversity statements and up to a third of participants are from backgrounds underrepresented in medicine.

"This is a very research heavy program. We are looking for students who have the research focus and logical thinking ability. You need to think deep to be scientists of the future. That's what we are trying to identify early and nurture," says Ray, associate professor of radiation oncology.

Students spend 10 weeks working in the lab of a U-M faculty mentor and cancer center member. The days are long and intense, but the payoff is big. Students will often publish the work they complete during the program, and all present their work at the end of the summer.

Giving students exposure to research career options also can help develop more diverse thinking in the field. **Sarah Steiner**, who is pursuing a Ph.D. at U-M in cell and developmental biology, started off as an engineering major.

"I didn't know research was available to me. If I had known in high school that I could use these logical thinking skills in a field with direct impact on human health, I would have pursued that earlier. I was an OK engineer. I'm a much better biologist," says Steiner, who co-leads BioMed Focus.

Giving Back And Engaging Community

Many of the summer programs create a virtuous cycle, engaging graduate and post-doctoral students to serve as mentors, speakers and leaders.

"As a first-generation student, I was never made aware of opportunities as early as I wanted to be. I have always wanted to give back in that capacity. I feel like I have so many resources. I want students to come away thinking science is cool, but I also want to reassure them that STEM is a space where they can belong," says **Gabrielle Rozumek**, a graduate student in molecular and cellular pathology and Developing Future Biologists instructor.

DFB rotates graduate and post-doctoral student leaders through a two-year commitment. Each new leader brings new ideas, which has morphed the program over the years.

In CaRSIP, cancer biology students lead weekly grand rounds-style talks, which Ray says has been more successful at engaging summer students.

"When faculty are talking, the students don't open up. When I bring in the cancer biology graduate students, it creates better energy and engagement," he says.

Angela Tuckowski, a doctoral candidate in cellular and molecular biology, remembers hating science lab classes until she worked in a research lab her sophomore year in college. When she learned about BioMed Focus, she raised her hand to mentor a student. She sees how these high schoolers are ahead of the game. But the experience also energized her.

"Going into your fifth year of grad school, you start to zone out and just think about what needs to get done. You forget why you even chose to do this. My mentee was bright-eyed and thought everything in the lab was so cool and interesting. It was refreshing to see, and it helped restore my own excitement for research," she says.

The TrEC team also collaborates closely with Rogel's

Summer training programs offered at Rogel

BioMed Focus
- High school students from Ypsilanti and Belleville
- 8 weeks researching in laboratories; participants present their work at the end of the program

SHE Oncology
(Summer Healthcare Experience in Oncology)
- Michigan high school students with demonstrated commitment to gender diversity, coordinated by American Cancer Society
- 2-week virtual program with speakers from all participating institutions, covering cancer research, health care, personal development

Cancer Research Summer Internship Program
(CaRSIP)
- Undergraduate students nationwide with strong interest and experience in research
- 10 weeks working in the lab with weekly lectures from Cancer Biology graduate students; participants present their work at the end of the program

Pathways Fellowship
- Undergraduate students from Michigan colleges and universities
- 2-week virtual program featuring talks by Rogel faculty, staff and trainees in various roles; participants present on a project at the end of the program

Developing Future Biologists
- Undergraduate students throughout North America whose educational or economic backgrounds are underrepresented in medicine
- 1-week intensive working in the lab; continued mentorship

Oncology Summer Internship
- Second-year medical students from U-M, coordinated by the American Society of Clinical Oncology
- Shadowing Rogel faculty in clinic plus virtual meetings with all participating cancer centers through ASCO

Medical student Michael Allevato, Ph.D., shadowed Lori Pierce, M.D., as she met with patients as part of the Oncology Summer Internship.

Community Outreach and Engagement mission, connecting with the catchment area the center serves. In Pathways, for example, students were asked to help large statewide research programs better recruit participants in their communities. Several of the suggestions, from Instagram accounts to radio stations to local bulletin boards, have been taken up by the research teams.

"These students are in our catchment area, whether they were born there or just going to school there. They are part of their school's larger community and can spread the mission of Rogel and help us with our research," Hawley says.

Creating A Network Of Long-Term Connections

The programs give students an intense experience during the summer, followed by a lifetime of connections.

"Networking is a key part of this," Henry says about the Oncology Summer Internship. "Students get the opportunity to meet faculty they wouldn't have otherwise met and get exposure to fields they hadn't thought about."

The medical student participants attend ASCO's annual conference in June, where they go to sessions and meet other participants and clinician-researchers.

"It was a bit overwhelming at first, given the vastness of the event and the variety of presentations," OSI participant **Michael Allevato, Ph.D.**, says about about the ASCO meeting. "However, it proved to be an exceptional learning opportunity. The discussions I engaged in and the knowledge I gained have been instrumental in shaping my understanding of the field."

Developing Future Biologists places heavy emphasis on building relationships and continuing to engage with previous participants. Many come back in later years to teach or present. Organizers keep close track of participants as they progress through graduate studies.

"We spend a lot of time selecting the people we think we can help the most. Developing Future Biologists is not only a one-week course but a commitment for after. We keep in touch with students, we network for them, we are a resource for them," says DFB instructor **Ligia B. Schmitd, Ph.D.**, a post-doctoral fellow in cell and development biology.

In all programs, faculty and trainees end discussions by providing their contact information and inviting students to reach out.

"It's been awesome that after every conversation with every person, they've said 'You can email me, you can ask questions,'" says Copeland, from the Pathways Fellowship. "I never felt like I had those connections until now."

What the Students Say

Michael Allevato, Ph.D.
Oncology Summer Internship

"I've had the chance to learn, grow and understand the complexities of cancer biology and patient care. My interactions with patients have reminded me of the very real, human side of this scientific pursuit. I look forward to continuing on this path and working towards my goal of becoming a physician-scientist in oncology."

Leah Arbitman
CaRSIP

"Coming into this program, I was unsure of my future plans. Now I know I'm definitely interested in research. I love how it's never the same. It's a very dynamic type of career and you get to study what you are passionate about every day."

Kelly Chambers
BioMed Focus

"The BioMed Focus program has equipped me with a number of lifelong skills that are going to be applicable to my future career in science. The college prep classes and science communication lectures have allowed me to scope out a clear plan for college and have shown me all that the University of Michigan provides. This program has been an incredible experience for me."

Jack Dawson
Pathways

"I liked hearing from the M.D.'s who do 80% research, 20% clinical. I thought that was only possible for someone with a Ph.D. I want to go to medical school but I'm interested in research. It's cool to realize there are ways to get involved without getting a Ph.D."

Ellee Kloian
BioMed Focus

"At the beginning of the program, I was a bit overwhelmed by hearing new terminology, meeting lots of academically impressive people, and being in a foreign place in general. However, everyone I met was not only excited to welcome me into the science world, but willing to take the time to explain complex topics to me even though it may be second nature to them. The people I met through the lab were very excited to teach me about what they were researching."

Abhishek Mahesh
CaRSIP

"Going into the program, I was already starting to apply to medical school. I always wanted to pursue research as well but was going down the path of being a clinician first and foremost. This program has focused my interest in research and pursuing an academic setting that will allow me to do clinical care and research at the same time."

CaRSIP students Leah Arbitman, Abhishek Mahesh and Navya Valvala

Faith Prentiss
Pathways

"I liked hearing everyone's stories about how you don't always end up where you thought you would be. I love lab work, but I don't love all the lab work I'm doing. I like hearing about other options. You don't have to take the traditional route to get where you're going."

Sherlyn Sanchez
Developing Future Biologists

"Following what I learned in this program, I've been able to attend scientific conferences, understand scientific articles and even land a lab internship in a different country. It helped me discover my identity in a science environment and feel proud of my non-traditional student background to continue inspiring others."

Navya Valavala
CaRSIP

"The research experience has definitely given me more perspective of what a Ph.D. student and a research scientist's life would look like. This program showed me how much failure is involved in research, and how it makes the high points even higher."

Collaborative Excellence

Rogel has become a center of excellence in pancreatic cancer research, combining pioneering research with innovative clinical care and an array of clinical trials. Marina Pasca di Magliano, Ph.D., explains why the key to a robust research program and responsive care lies in collaboration.

By Anna Megdell

After 15 years of running a lab at the Rogel Cancer Center, **Marina Pasca di Magliano, Ph.D.**, has become one of the world's leading researchers on pancreatic cancer.

She and her collaborators run a team of researchers, including postdoctoral fellows, clinical fellows, graduate and undergraduate students, who study how pancreatic cancer develops and interacts with the tumor microenvironment to grow and resist treatment. They examine the disease from a genetic, metabolic and immune perspective, taking a multidisciplinary approach to determine which factors contribute to the disease's aggressive nature.

Pasca di Magliano is quick to point out that her lab doesn't work in isolation. As part of Rogel's Pancreatic Cancer Working Group, her lab is a vital part of a dynamic ecosystem of basic scientists and clinicians who share data and ideas to learn about and ultimately attack the disease.

Here, Pasca di Magliano, Maud T. Lane Professor of Surgical Immunology, discusses the collaboration that makes Rogel's pancreatic cancer team unique. ↬

How has Rogel cultivated such an expertise in pancreatic cancer?

There's a combination of factors, one being targeted hires across departments. Basic science researchers, translational researchers and many clinicians who are actively involved in research. Another thing that might seem simple but makes a huge difference: many of us have labs next to each other, on the sixth floor of the Rogel Cancer Center building. It allows for an exchange of ideas, joint mentoring of trainees and a lot of collaboration.

This connection is further catalyzed by our working group meetings that happen every Friday morning and have been going on for years. I travel around the country quite a bit to give talks and of the many other places with multiple researchers who study pancreatic cancer, I don't know of any other place that has a weekly joint lab meeting that is well attended and interactive.

Our group involves more than 10 laboratories across six departments. In addition, we ran as a hybrid meeting even before the pandemic, with collaborators from the University of Western Ontario and Henry Ford Health.

With everybody working together, we've been able to work on larger, high impact projects that would have been above the ability of any one laboratory. We have proven our weight by successfully competing for funding, including multiple R01 grants and collaborative grants such as a U01 that is part of the Pancreatic Cancer Stromal Reprogramming Consortium consortium and a U54 that is part of the Translational and Basic Science Research in Early Lesions Consortium and involves investigators at MD Anderson and Johns Hopkins.

It takes everybody being willing to realize they can't always be first. It's a shared mindset of, "It's not all about me. It's about the research, training and patients." I do think the fact that we have so many clinicians involved in research is part of our success, because they are directly involved in patient care. That helps us keep in perspective that everything we do is about patients, about preventing, detecting and treating pancreatic cancer. We don't want to lose that perspective. Our joint group of physicians and researchers helps us keep the patients front and center.

Pancreatic Cancer Working Group Collaborators

Department of Surgery: Timothy Frankel, M.D.; Filip Bednar, M.D., Ph.D.; Donnele Daley, M.D.; Peng Zhang, Ph.D.

Department of Molecular and Integrative Physiology: Costas Lyssiotis, Ph.D.

Department of Internal Medicine: Vaibav Sahai, M.D., M.S.; Eileen Carpenter, M.D., Ph.D.

Department of Pathology: Jiaqi Shi, M.D., Ph.D.

Department of Pharmacology: Kyoung Lee, Ph.D.

Department of Computational Medicine and Bioinformatics: Arvind Rao, Ph.D.

Based on yours and your Rogel colleagues' work, where do you see pancreatic cancer research going? Is there an area of focus that might yield the most information or unlock the most potential?

The research is moving toward a more personalized oncology approach, really understanding how each tumor is different and how tumors change during treatment. We have to respond to each patient's disease, not just initially but throughout treatment. A key source of new understanding will be trials that focus on longitudinal sampling of tumors to detect how they respond to treatment and understanding the avenue of recurrence. At the same time, it will be important to get a sense of a patient's status over the course of their treatment through blood samples. This area of research is different from biomarker research. Instead of comparing a patient to a whole sample population, you follow the individual patient over time, throughout their treatment and after. It can help us pinpoint when they stop responding to treatment or when they've developed resistance.

We're also working toward a combination of a metabolism and immunity approach, especially through examining mutant KRAS, the key oncogene of pancreatic cancer that regulates the tumor microenvironment. The ultimate goal is to get an immune response to the tumor. I strongly believe that's the only way we will get long-term control over the disease. There's a lot of data from people who do survive a long time and have mounted an immune response to cancer. But it just happened on their own. We want to know how to optimize that. How can we get more patients to develop that immunity?

What does a center of excellence mean to you? What elevates a research institution to being a destination for patients?

Obviously top-notch clinical care, as well as comprehensive care. The lab-to-clinic pipeline is important. We have the ability for patient samples to be used in lab research. Then the knowledge we gain in the lab goes back to oncologists, who can bring that knowledge to other patients. It's also vital to have a robust clinical trial program. Rogel is part of an initiative called Precision Promise, which is led by the Pancreatic Cancer Action Network. It's a flexible way to have patient-specific clinical trials here, so patients can be enrolled in whatever protocol is best for them. Otherwise, we would offer just one trial here, and if patients did not qualify, they would be excluded from research. It will allow us to increase the number of patients that enter clinical trials for pancreatic cancer.

How do you interpret the idea of *following the science* in the context of pancreatic cancer research?

I tell my students all the time and want them to understand that, in research, we try new things and will probably be wrong a lot of the time. But we train ourselves to follow the data and go where the data takes you. We had a grant from the American Cancer Society that was initially meant to study the role of regulatory T cells, which are inhibitory immune cells, and it ended up funding some sequencing work instead. We had this very well-crafted hypothesis, and in some ways it was a boring idea: You take away the cells that inhibit the immune response, the immune system gets activated and the tumor goes away. Well, what actually happened when we did this in mice was that the disease got worse. And we couldn't make sense of it. It took us a long time to figure out what was happening. We discovered that if you take away regulatory T cells, you end up with a cascade of changes in the tumor microenvironment, which are all the types of cells that are in a tumor, not just cancer cells. Bottom line, what happens is that you block the immune system, but it also brings in some cells that directly make the tumor grow faster.

It was a finding that made no sense that we could have just brushed under the rug and said, "It doesn't work, let's move on." Instead, we knew this was what we really had to pursue and understand. It's one of my favorite papers from the lab.

What do you want people to know about the Pancreatic Cancer Working Group?

We've been very successful with developing trainees and junior faculty. They've received major grants and professorships and have created their own independent labs. Three of our recent postdoctoral trainees, **Christopher Halbrook**, **Nina Steel** and **Zeribe Nwosu**, obtained K99/R00 grants from the NCI and successfully obtained tenure track or equivalent faculty positions at the University of California Irvine, Henry Ford Health Systems/Michigan State University and Cornell University. A former clinical fellow, **Eileen Carpenter, M.D., Ph.D.**, is now an assistant professor in internal medicine at the University of Michigan and a member of the team. Training is key to what we do. And we have a strong emphasis on diversity. Our labs are incredibly diverse, including nationality, race, background, geography. We include many first-generation college students. We have to have a strong commitment to career development. The future of research depends on it.

"Think of enhancers as bookmarks. They mark pages in the genetic book that contain cell type-specific DNA information."

Abhijit Parolia, Ph.D.

Uncovering Cancer's Roots in Chromatin

Growing PARLAB looks to gene architecture for novel cancer therapies.

By Staci Vernick

Abhijit Parolia, Ph.D., recalls the first moment he heard the question that would come to define his entire scientific career. One of 21 undergraduate students fortunate enough to have secured a place in the highly competitive joint honors biotechnology program at the University of British Columbia/British Columbia Institute of Technology, Parolia was intrigued when a professor asked, what is a gene?

In October, the molecular biologist launched his own independent lab as a tenure track assistant professor at the Rogel Cancer Center. The Parolia Lab—or PARLAB as he calls it—studies the role of chromatin in cancer and how its architecture may be exploited to develop new therapies. Chromatin is the tightly wound package of DNA and proteins in the nucleus of every human cell that drives transcription and gene expression.

"My work centers on uncovering cancer's root in the chromatin," Parolia explains. "What are these roots, how deep are they, and how do we find ways to uproot this disease, starting from the soil, i.e., the DNA."

Parolia began his University of Michigan journey in 2015 as a graduate student in the laboratory of internationally renowned prostate cancer researcher **Arul Chinnaiyan, M.D., Ph.D.**, director of the Michigan Center for Translational Pathology at Rogel.

In the Chinnaiyan Lab, Parolia studied FOXA1, a specialized transcription factor or protein essential for normal development of the prostate that is frequently mutated in prostate cancer. Parolia and colleagues defined the biological mechanisms through which FOXA1 initiates prostate cancer and causes it to grow and spread. The work, published in *Nature* and the foundation of Parolia's dissertation, set the stage for the development of new cancer therapies targeting FOXA1's activity.

Parolia graduated the U-M Medical School in 2021 with a dual Ph.D. and master's in molecular and cellular pathology and bioinformatics but didn't follow the conventional route to a postdoctoral fellowship. Instead, he was offered a junior faculty position at U-M as a research investigator within the Department of Pathology under the mentorship of **Weiping Zou, M.D., Ph.D.**, director of Rogel's Center of Excellence for Cancer Immunology and Immunotherapy. For the next two years, he worked with Zou to understand how chromatin in immune system T cells changes when they recognize and attack cancer cells.

The growing Parolia Lab at Rogel focuses on the architecture of chromatin and transcriptional abnormalities in hormone-driven cancers, such as prostate and breast cancer.

Every cell in our bodies contains the exact same strands of DNA, tightly wound around proteins called histones into fundamental units called nucleosomes. This genetic package is collectively known as chromatin.

Lineage commitment determines whether a cell will function in vision as an eye cell or in sexual reproduction as a prostate cell. That commitment—the functional fate of any cell—is governed by enhancers, specialized non-coding regions on a strand of DNA that bind proteins to activate gene functions. These non-coding DNA elements get specifically opened in different cells to enable the gene transcription that ultimately determines the function of the cell.

"Think of enhancers as bookmarks," Parolia says. "They mark pages in the genetic book that contain cell type-specific DNA information."

Parolia, recently appointed as a Rogel fellow, says cancer hijacks and amplifies the normal enhancer pathway machinery of lineage commitment.

"We need to understand how these protein complexes that are binding on specific enhancers are different in cancer than in normal cells. What are the proteins at work, what is the sequence of their assembly?" he asks. "Most importantly, can these keystone proteins be targeted to break this hijacked cancer-specific enhancer pathway to have therapeutic benefit?"

As he pursues these questions in his own lab, Parolia continues to collaborate with his mentors at Rogel.

"Modern day science is impossible to do alone. To be at the edge of the translational field, doing high impact research, you've got to have a multidisciplinary team that supports and enables the science. That's what we have at Michigan and at Rogel."

Photo: Michigan Photography

Cracking the Code of RNA

A perspective shift in college led Amanda Garner to chemistry. Now, her cutting-edge research explores RNA-targeted therapeutics for cancer and other diseases.

By Staci Vernick

Growing up in rural St. Marys, Pennsylvania, where the high school science curriculum was lean, **Amanda Garner, Ph.D.**, set her practical career sights on medicine or accounting. With no role models in her small town, it never occurred to her to think of becoming a scientist.

Things changed in college. A chemistry professor recognized the pre-med major's potential and offered her an opportunity to work in a chemistry lab.

"I had never considered chemistry at all in my life," Garner says. "But when I got to organic chemistry I thought, oh, this is what it's all about!

"Because you see the structures of drugs, what a molecule looks like in three-dimensional space," she continues. "It's quite incredible to think about how that's interacting with us once inside our bodies."

Garner went on to earn her Ph.D. in chemistry from the University of Pittsburgh then spent time as a postdoctoral fellow and research associate at the Scripps Research Institute. There, her research interests moved into the emerging field of RNA biology. She joined the University of Michigan as an assistant professor in 2013.

Today, the Garner Lab at Rogel is celebrating its 10th year working at one of the final frontiers in drug discovery—the search for and development of RNA-targeted therapeutics for cancer and other diseases.

The lab's core focus is exploring RNA biology. The Human Genome Project found that while a tiny percentage of the genome encodes for proteins—typically considered the building blocks of life—more than 98% of it encodes for non-coding RNAs which have been linked to nearly all diseases, from cancer to Alzheimer's to diabetes.

"RNA biology is a great, wide-open space for a chemist to play because we can find molecules that can be developed as drugs or as probes to uncover the basic biology of what these molecules are doing in diseases like cancer, where RNA becomes dysregulated," she explains.

"That is what the next generation of drug discovery looks like."

Garner's interdisciplinary lab of 12 members uses chemical biology, medicinal chemistry, and molecular and cellular approaches to investigate targeting RNAs and RNA-protein interactions for probe and drug discovery. Current projects focus on validating and discovering new targets to promote the emerging field of RNA-targeted drug discovery.

An associate professor of medicinal chemistry and director of the Interdepartmental Program in Medicinal Chemistry within U-M's College of Pharmacy, Garner enjoys teaching and mentoring graduate students. She pushes her students to use their imaginations, take risks and follow the science to the next big problems.

What does the future hold for Amanda Garner?

"Cracking the code of RNA," she says, laughing. "As we've become more interdisciplinary, I'm optimistic that we'll be able to answer the questions we didn't at first have the tools for."

Working in cancer models, "we can now see the impact of the transcriptome and use that information to better patients' lives. That's the overall goal."

Photo: Leisa Thompson

The Importance of Being Flexible

Medical director of Clinical Research Specimen Processing Paul Swiecicki reflects on his unexpected journey to hematology and oncology.

By Eric Olsen

Career paths are often full of unexpected bends and twists—but that's not necessarily a bad thing. When **Paul Swiecicki, M.D.,** was in medical school, he planned to pursue a career in neurology. Reflecting on that time now, his path didn't quite play out in the way he expected. "Through one twist and then another, I realized that hematology and oncology was the perfect fit for me, for multiple reasons, including the patient population, unmet need and research interests. I haven't looked back since," he says.

For Swiecicki, the twists became the norm rather than the exception. "Medical education and research tend to follow a linear path," he says. "For example, after medical school we proceed to a residency, then a fellowship, then become a faculty member that specializes in a single disease. Or, if you are involved in research, you are categorized as performing either clinical or lab-based research. We don't really talk about the ways careers can evolve in an organization like Rogel. I've been surrounded by amazing people and given great opportunities that I wouldn't have seen. You take those opportunities as they come. Being flexible is very important."

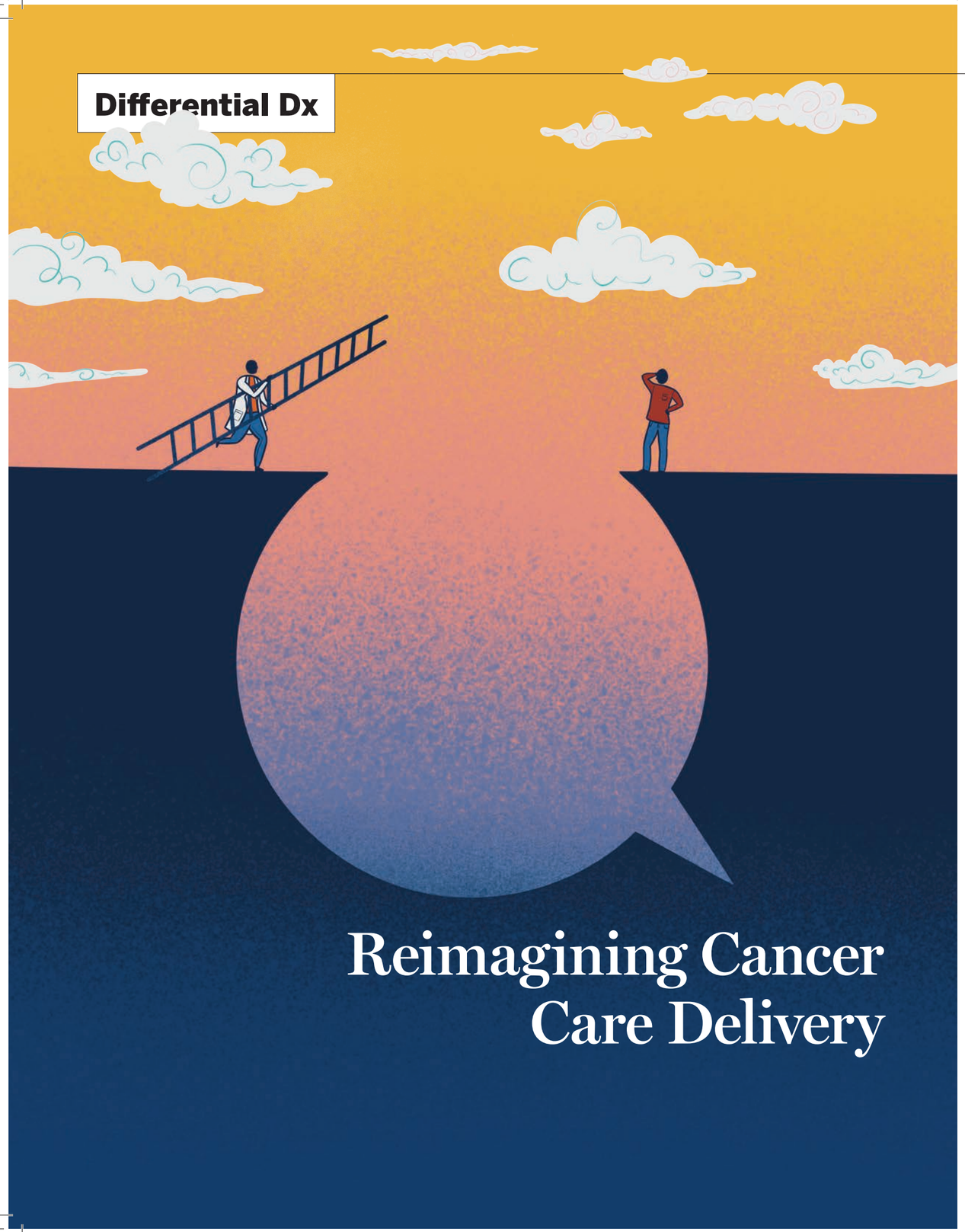
In March 2022, Swiecicki was named medical director of Clinical Research Specimen Processing (CRSP), where he oversaw the lab's expansion into a larger space with more processing capacity. This past January, he was named inaugural associate medical director for the Oncology Clinical Trials Support Unit (O-CTSU). The O-CTSU serves as the centralized core facility of all cancer-related clinical research trials conducted by investigators throughout Michigan Medicine.

Swiecicki is quick to acknowledge his colleagues and mentors. "Although I'm very proud of where I'm at, many I've worked with deserve a great deal of credit. The staff of the O-CTSU and CRSP make clinical research possible daily. Without them, we would not be able to offer options to patients or have participated in groundbreaking trials.

"And I'm very grateful to the medical director of the O-CTSU **Scott Schuetze, M.D., Ph.D.** He's been a great colleague and I'm learning a lot from him."

For Swiecicki, clinical work is critical. Central to everything he does is advancing patient care and the betterment of patients. "Too many patients are suffering with cancer, as are their families," he says. "So, I believe at the end of the day—be it via discovery of a new cellular pathway, drug delivery system, biomarker or even clinical trial—our work should return to the singular goal of helping ameliorate the burden of cancer. It has been very exciting to see some of our research projects come to fruition and our work make a tangible difference. There are people who were thought to be incurable, and now years later are living normal lives without evidence of cancer. Those are the kinds of stories that really drive us."

Photo: Erica Reist Bass



Reimagining Cancer Care Delivery

Patients with limited English proficiency face extra barriers to care. Here are ways we can do better.

Debbie W. Chen, M.D.
Clinical Instructor of Metabolism, Endocrinology and Diabetes

A new cancer diagnosis can create many challenges throughout a patient's cancer journey. Overcoming barriers to accessing cancer care should not have to be one of them.

However, this is the reality for the more than 25 million individuals in the United States with limited English proficiency who have limited ability to read, speak, write or understand English.

Research shows that language discordance between patients and physicians negatively impacts the quality of patient care. Linguistic disparities also exist in patients' access to health care services, including cancer care. A major contributor is that our current health care system is designed with the English-proficient patient in mind.

Current State of Health Care for Limited English Proficient (LEP) Patients

Patients access cancer care services through a series of critical steps, beginning with finding the appropriate cancer clinic. Unfortunately, even at this early step, linguistic barriers make it difficult, and sometimes impossible, for LEP patients to access cancer care services.

Prior work by our team found that at the level of the hospital operator, non-English-speaking simulated patient callers had lower odds of being provided with the telephone number or being transferred to the clinic for the requested cancer care service compared to their English-speaking counterparts.

Similarly, other studies have demonstrated that at the critical step of scheduling a new patient clinic appointment, Spanish-speaking simulated patient callers were less successful compared to their English-proficient counterparts.

On the day of the clinic appointment, LEP patients may be accompanied by a bilingual family member (who has not been trained in providing language interpretation but whose role it is to facilitate communication with the health care team) or depend on language services offered by the clinic or hospital.

Unfortunately, the availability and use of language services in hospitals nationwide is variable. A study from 2013 reported that 31% of hospitals did not offer any language services. When language services are offered, LEP patients may be connected with a language interpreter (often via a landline phone on speaker mode) in the public waiting room while checking in and checking out for their clinic appointment and after getting roomed by a medical assistant.

Cancer Care Delivery Reimagined

Scheduling A New Patient Appointment
In 2020, Medicine Medicine Interpreter Services developed the Patient Access Line, which is a 24/7 telephone service that LEP patients "can use to contact Michigan Medicine to discuss anything related to their care within our institution." Expansion of this service at U-M, and development of similar programs at other institutions, could reduce the linguistic barriers at the level of the hospital operator and at the critical step of scheduling a clinic appointment.

Interventions are also needed to address systems-level barriers to appointment scheduling, such as the requirement for patients to obtain a referral for cancer care services and submit relevant outside hospital records prior to being offered a clinic date. Navigating these hurdles present unique difficulty for LEP patients. With the technological advances available today, this process can be streamlined and the administrative burden on patients decreased.

Day of Appointment
Prior to the COVID-19 pandemic, it was not uncommon for LEP patients to arrange for Michigan Medicine interpreters to meet them at their clinic appointment. In addition to facilitating communication between patients and their clinician, the interpreter was able to assist the patient in navigating the check-in and check-out processes, walking to and checking in at the laboratory if blood work was ordered, and interacting with other staff

Thus, it may be beneficial to offer all LEP patients the option to have a professional language interpreter present at their cancer appointment to facilitate a smoother, less fragmented transition between the varied components of the clinic visit, of which the patient-clinician interaction is just one part.

Access to Cancer Clinical Trials
Beyond the clinic visit, an important component of cancer care is access to cancer clinical trials, which have historically enrolled very low percentages of racial and ethnic minorities. This lack of diversity in clinical trials limits the generalizability of study findings, which has the potential to impact which novel therapeutics are approved for treating cancer in the real-world setting.

While the lack of diversity is multifaceted, linguistic barriers are potentially a significant contributing factor in the enrollment of Hispanic and Asian patients, two groups with the highest rates of limited English proficiency (35%) in the United States. Thus, to increase the recruitment and enrollment of these two patient populations into cancer clinical trials, it is important to translate relevant forms into non-English languages, hire diverse clinical trial staff from these communities, and have resources available for patients facing cancer-related financial hardship, which is greater among patients from racial and ethnic minorities.

The burden of cancer disparities disproportionately impacts the health of racial and ethnic minorities, including those with LEP. Access to cancer care for many patients is limited by linguistics and systems-level barriers that need to be addressed. With more than 60 million individuals in the United States speaking a language other than English, it is time to rethink how we can best deliver cancer care so that all patients, regardless of English language proficiency, have equitable access.

Illustration: Ananda Walden

Spotlight

Rogel Cancer Center's NCI designation renewed

THE NATIONAL CANCER INSTITUTE renewed the Rogel Cancer Center's "comprehensive cancer center" status and awarded the center a grant worth $37 million over five years.

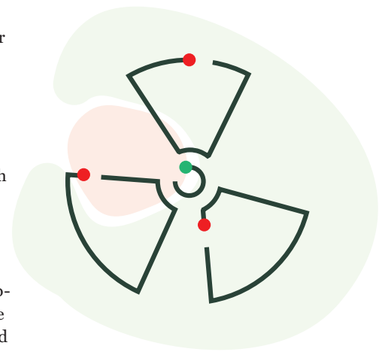
The grant is a renewal of the Cancer Center Support Grant, provided as part of the NCI's cancer centers program. Rogel first received NCI designation in 1988 and was designated comprehensive just three years later. The new grant provides funding through 2028, extending Rogel to 40 consecutive years of funding. The $37 million represents a 10% increase over the previous support grant.

"We are thrilled that the National Cancer Institute reviewers recognized the Rogel Cancer Center's distinguished history of scientific excellence, collaboration and impact. This cancer center support grant renewal will enable us to do even more to reduce the burden of cancer throughout Michigan and beyond," says **Eric Fearon, M.D., Ph.D.**, director of the Rogel Cancer Center.

Rogel awarded SPORE grant to further research on radiosensitization

ROGEL RESEARCHERS received an $11 million grant from the National Cancer Institute to further research on radiosensitization, the process of making tumors more vulnerable to radiation treatment.

The grant, led by principal investigators **Meredith Morgan, Ph.D.**, and **Ted Lawrence, M.D., Ph.D.**, is funded through NCI's Specialized Program of Research Excellence. While SPORE grants are typically awarded to projects focused on a specific disease, this grant centers around radiosensitization as a cancer treatment approach, looking at how specific drugs make radiation more effective in locally advanced pancreas, brain and breast cancers.



U-M partners with Singapore hospital, cancer center

THE UNIVERSITY OF MICHIGAN is developing two academic and scientific partnerships in Singapore to create opportunities for joint research, and trainee and student exchange. Partnerships are with the National University of Singapore's Cancer Science Institute and the National University Cancer Institute, Singapore. The other partnership is between the Rogel Cancer Center and the National Cancer Centre Singapore.

Rogel earns re-accreditation from Commission on Cancer

THE ROGEL CANCER CENTER was re-accredited by the Commission on Cancer, a quality program of the American College of Surgeons. To earn accreditation, a cancer program must meet 34 CoC quality care standards, be evaluated every three years through a survey process, and maintain levels of excellence in the delivery of comprehensive patient-centered care.

Rogel was first accredited by CoC in 1932, making it one of the first cancer programs to receive accreditation.

Rogel and IHPI award 2 policy sprint awards

THE ROGEL CANCER CENTER and Institute for Healthcare Policy and Innovation awarded cancer-specific Policy Sprints awards to inform health policy or practice at the local, state, national or global levels:

- Effect of the 340B drug pricing program on advanced prostate cancer care. **Kassem Faraj**, M.D.; **Vahakn Shahinian**, M.D., M.S.; **Lindsey Herrel, M.D., M.S.**
- Evaluating out-of-pocket cost variability of cancer medications insured by Medicare Part D plans. **Kristian Stensland**, M.D., M.P.H., M.S.; **Ben Pockros**, M.D., M.B.A.; **Chad Ellimoottil**, M.D., M.S.; **Megan Caram**, M.D.

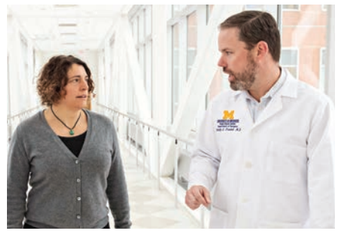
U-M Health launches mobile mammography unit for breast cancer screening

THE UNIVERSITY OF MICHIGAN HEALTH began offering mammography screening services through a new mobile mammography unit. The unit is scheduled regularly at the Ypsilanti Health Center and travels to select locations statewide to increase access to cancer care and provide screening opportunities for patients near their homes.

"We believe that providing care closer to the community improves access and opportunity for earlier care, diagnosis, treatment and recovery of health. Our mobile mammography unit and radiology team will bring these services directly to the community, making it easier for our patients to access care," says **Tony Denton, J.D., M.H.A.**, senior vice president and chief environmental, social and governance officer of U-M Health and Michigan Medicine.

Lee receives $1.4M to study the role of low oxygen supply in pancreatic cancer

Kyoung Eun Lee, Ph.D., received $1.4 million from the National Cancer Institute to study how hypoxia in pancreatic cancer alters the tumor-stroma interaction – and how to capitalize on that to target potential new treatments. The grant will allow Lee to explore how hypoxia makes the tumor microenvironment resistant to immune therapies.



Rogel researchers receive $2M to study pancreatic cancer microenvironment

Marina Pasca di Magliano, Ph.D., and **Timothy Frankel, M.D.**, received $2 million from the National Cancer Institute to understand the role myeloid cells play in how pancreatic cancer develops and progresses. They will use patient tissue samples and genetically engineered mouse models to map myeloid cell populations and functional status in the healthy pancreas, PanIN and pancreatic cancer.

Rogel researchers get $3 million to improve survivorship care for younger colorectal cancer patients

Lauren Wallner, Ph.D., M.P.H., and **Pasithorn Suwanabol, M.D.**, received $3.07 million from the National Cancer Institute to develop a model for long-term surveillance and care of younger adults treated for colorectal cancer. They will identify patterns of recurrence among younger patients diagnosed with stage 1-3 colorectal cancer to understand survivors' risk of recurrence, including the clinical and sociodemographic factors impacting that risk.

Rogel researchers receive $4M from Prostate Cancer Foundation

ROGEL RESEARCHERS led by **Arul M. Chinnaiyan, M.D., Ph.D.**, received a $4 million Prostate Cancer Foundation TACTICAL (Therapy ACceleration To Intercept CAncer Lethality) Award. The project will employ a suite of cutting-edge drug development techniques to develop an effective inhibitor of MYC, a major driver of about 70% of all cancers, including prostate cancer.

Kim receives Research Specialist Award from NCI to advance clinical trials

Michelle Kim, M.D., received a Research Specialist Award from the National Cancer Institute to pursue clinical research efforts. Kim's focus is on clinical research for central nervous system tumors. She has developed and led five investigator-initiated studies and enrolled 165 patients to trials since 2015. ➔

Castro inducted into AIMBE College of Fellows

Maria G. Castro, Ph.D., was inducted to the American Institute for Medical and Biological Engineering College of Fellows, which comprises the top 2% of medical and biological engineers. Castro was nominated, reviewed and elected for her contributions to the brain tumor field, development of immune-engineered nanomedicines and gene therapies for brain cancer, and for mentoring women and minorities.

3 Rogel faculty receive Biosciences Initiative award

Three Rogel Cancer Center faculty members were named 2022 winners of the annual Mid-career Biosciences Faculty Achievement Recognition Award, which recognizes exceptional mid-career faculty in the biosciences. The awards provide $250,000 per year for two years in discretionary funds to encourage innovative, high-risk research. The Rogel awardees are:

- **Jianping Fu, Ph.D.**
- **Costas Lyssiotis, Ph.D.**
- **James Moon, Ph.D.**

Harper elected to Association of American Physicians

Diane Harper, M.D., M.P.H., M.S., was elected to the Association of American Physicians, a top honor in science and medicine that recognizes researchers who have made impactful contributions to improve patient care through the advancement of physician-led research. Harper has significantly advanced efforts in the prevention, early detection, and treatment of HPV and cervical cancers.

5 Rogel members named AAAS fellows

Five Rogel Cancer Center members were elected as 2022 fellows of the American Association for the Advancement of Science. AAAS, the world's largest general scientific society, selects fellows for their scientifically and socially distinguished achievements. The five are:

- **Thomas Carey, Ph.D.**
- **Joerg Lahann, Ph.D.**
- **Marina Pasca di Magliano, Ph.D.**
- **Donna Martin, M.D., Ph.D.**
- **Duxin Sun, Ph.D.**

Ten Haken receives ASTRO Gold Medal

Randall K. Ten Haken, Ph.D., was named a recipient of the 2023 ASTRO Gold Medal Award by the American Society for Radiation Oncology. Ten Haken is the sixth Gold Medal winner from the University of Michigan. The award, ASTRO's highest honor, is bestowed on revered members who have made outstanding contributions to the field of radiation oncology.

Chinnaiyan receives AACR award for cancer pathology

Arul M. Chinnaiyan, M.D., Ph.D., received the 2023 AACR James S. Ewing-Thelma B. Dunn Award for Outstanding Achievement in Pathology in Cancer Research from the American Association for Cancer Research. Chinnaiyan was cited for his research linking chromosomal abnormalities and cancer, including his discovery of TMPRSS2-ETS gene fusions in prostate cancer, and for pioneering the use of pathological and bioinformatic methodologies to diagnose and track prostate cancer onset and progression.

Mukherjee named Distinguished University Professor

Bhramar Mukherjee, Ph.D., was awarded the university's highest professorship of Distinguished University Professor, recognizing exceptional senior faculty and their contributions to academic excellence. Mukherjee is the John D. Kalbfleisch Distinguished University Professor, named after the former chair of biostatistics at the School of Public Health.

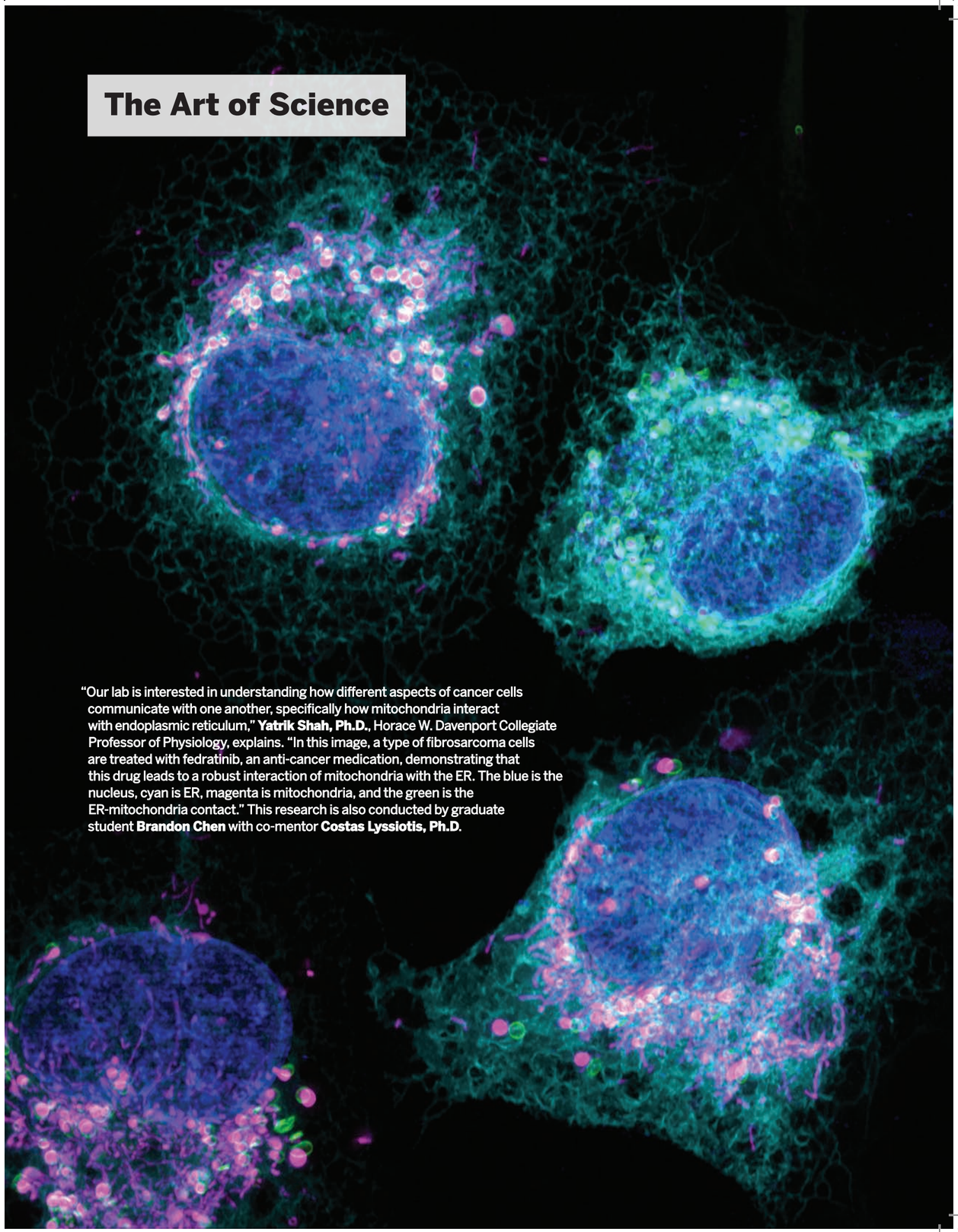
Rogel researchers receive funding to bring equity to AYA cancer research and outcomes

Anao Zhang, Ph.D., and colleagues received a $250,000 Eugene Washington PCORI Engagement Award, an initiative of the Patient-Centered Outcomes Research Institute, or PCORI. The research team will build out existing research infrastructure in patient-centered outcomes to enhance participation from adolescent and young adult cancer survivors who identify as BIPOC or sexual and gender minorities. Researchers have found outcomes for AYA patients differ based on race, ethnicity, sexual orientation and gender identity.

Scott gets $792K Discovery Science grant from American Cancer Society

As part of its Discovery Science grants program, the American Cancer Society awarded **Anthony Scott, M.D.**, $792,000 to look at how genes associated with Lynch syndrome impact cancer developing. With the grant, Scott will apply computational biology to look at cells with a variant of uncertain significance to understand how those cells repair DNA damage and when cancer progresses.

The Art of Science



"Our lab is interested in understanding how different aspects of cancer cells communicate with one another, specifically how mitochondria interact with endoplasmic reticulum," **Yatrik Shah, Ph.D.**, Horace W. Davenport Collegiate Professor of Physiology, explains. "In this image, a type of fibrosarcoma cells are treated with fedratinib, an anti-cancer medication, demonstrating that this drug leads to a robust interaction of mitochondria with the ER. The blue is the nucleus, cyan is ER, magenta is mitochondria, and the green is the ER-mitochondria contact." This research is also conducted by graduate student **Brandon Chen** with co-mentor **Costas Lyssiotis, Ph.D**.

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