

A large, vibrant fluorescence microscopy image of cells, likely cancer cells, showing various organelles and structures in shades of blue, green, yellow, and red against a dark background. The word "Illuminate" is overlaid on the top left of this image.

Illuminate

A Publication Highlighting the
Research at the University
of Michigan Rogel Cancer
Center

2020

**Shedding light
on cancer
biology,
treatment and
translation to
the clinic**



ROGEL CANCER CENTER
MICHIGAN MEDICINE

LETTER FROM THE DIRECTOR

As we enter a new decade, Rogel Cancer Center researchers continue to illuminate new aspects of cancer biology, move promising drug discovery projects toward the clinic and analyze outcomes data to improve care delivery. Thus, it is fitting that *Illuminate* is the title of our new annual research publication. The title reflects the intellectual curiosity and passion for discovery that motivates and inspires our faculty, staff and trainees. The core missions of our cancer center can be summed up as improve, inspire, impact and illuminate.

- Improve cancer outcomes for all patients, survivors and those at risk of cancer
- Inspire patients and families, faculty and staff colleagues, and the next generation of cancer pioneers and providers
- Impact the communities we serve in Michigan and beyond by providing improved access to outstanding clinical care and reduced cancer risk via outreach and education activities
- Illuminate how different cancers arise and progress, as well as new approaches to prevent cancer, detect it at its earliest and most curable stages, and treat it with more effective and less toxic therapies

The Rogel Cancer Center has more than 340 faculty members in 53 departments across the University of Michigan pursuing cutting-edge research. Our researchers have a multi-decade history of pioneering advances across the continuum of cancer research, including groundbreaking work that defines key genetic, cellular, lifestyle and environmental factors that underlie the origins and behaviors of cancer, along with contributions to the development of innovative approaches to prevent, diagnose and treat cancer more effectively.

Illuminate highlights some of our most significant advances, as well as places our new findings in the larger context of the cancer research and patient care landscape, and offers thoughts about potential new directions and opportunities to further advance and apply that knowledge for good.

Sincerely,

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

On the cover:

A single lung metastatic lesion in a mouse model of colorectal cancer, where there is evidence that multiple independent cancer cells from the primary tumor have contributed to the formation of the metastatic lesion.

Image by Ying Feng, Ph.D., and Jinyu Tang, an M.D., Ph.D. student

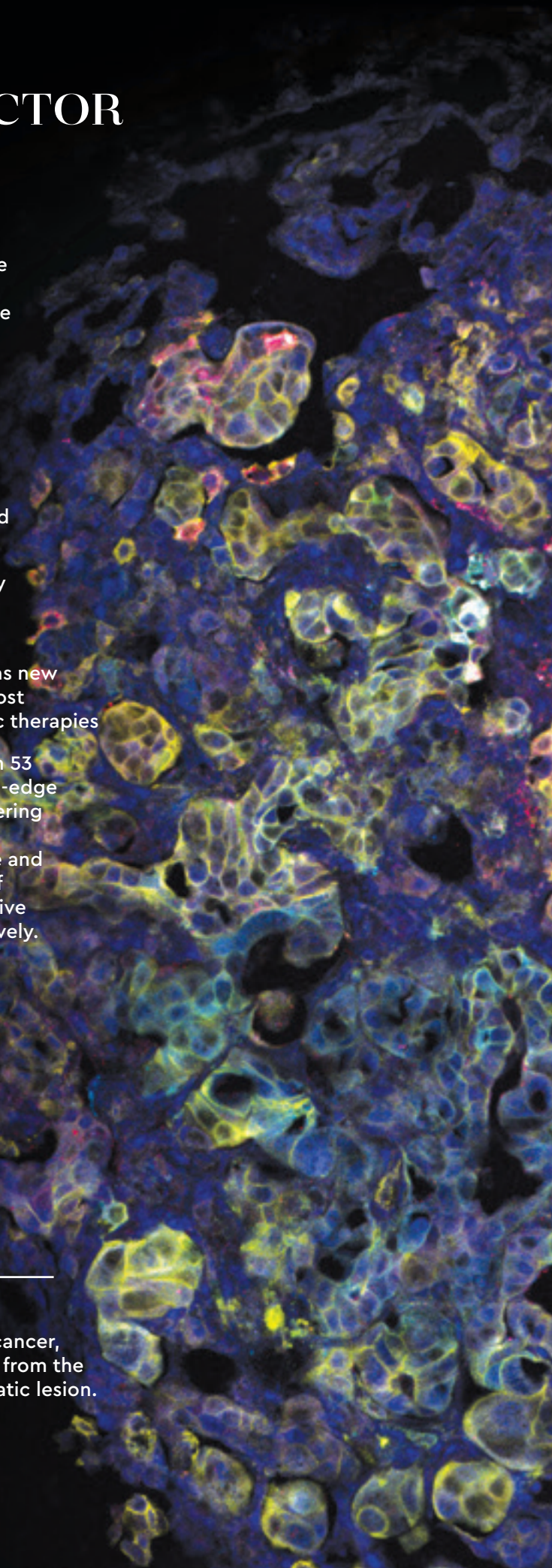


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Scientists of the Future

Strong mentorship and sponsorship leads to promising careers

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Harnessing the **Immune**

How cancer immunology moved from a fringe idea to one of the biggest game-changers in cancer treatment

BY NICOLE FAWCETT



Weiping Zou, M.D., Ph.D.



Shirish Gadgil, MBBS

WHEN WEIPING ZOU, M.D., PH.D., FIRST STARTED LOOKING AT CANCER IMMUNOLOGY, HE WAS ONE OF ONLY A HANDFUL IN THE FIELD THAT BELIEVED IN THE IDEA.

"PEOPLE DID NOT BELIEVE THE VERY EXISTENCE OF CANCER IMMUNITY. THE JOB OF THE IMMUNE SYSTEM SHOULDN'T BE TO ATTACK YOURSELF," RECALLS ZOU, CHARLES B. DE NANCREDE PROFESSOR OF SURGERY, IMMUNOLOGY, BIOLOGY AND PATHOLOGY AT THE UNIVERSITY OF MICHIGAN.

TODAY, IMMUNOTHERAPY HAS REVOLUTIONIZED CANCER TREATMENT AND BECOME ONE OF THE MOST PROMISING AVENUES IN CANCER RESEARCH.

A 3D rendering of PD-1 (blue) bound PD-L1 (red). Blockers of the PD-L1 and PD-1 interaction, including nivolumab and pembrolizumab, are an important new class of anticancer drugs.

System to Target Cancer

"It's as big a game-changer as you can imagine," says Christopher Lao, M.D., MPH, professor of hematology/oncology at Michigan Medicine, who sees patients with melanoma. "There are a number of patients now between five to eight years out with no disease and they're off treatment. I believe we are curing at least a subset of patients."

Rogel Cancer Center scientists are uncovering novel approaches in the laboratory to harness the immune system against cancer, and they are working with clinical researchers to translate these ideas into treatment strategies. At the same time, what they learn from patients goes back to the lab to piece together why these treatments work for only a small portion of patients — and how to expand their success to a larger number.

Fundamental understanding

It was a rocky start. Researchers hypothesized that cancer patients had weakened immune systems and that making the immune system stronger would solve the problem. The focus was on giving patients more T cells, the soldiers of the immune system that do battle against foreign invaders.

These strategies had limited success — but just enough to keep people believing immunotherapy could work.

"We thought this T cell supplementation strategy wasn't ideal. Maybe instead we needed to resolve something, find out what's blocking the immune system," says Zou, director of the Rogel Cancer Center's Center of Excellence for Cancer Immunology and Immunotherapy.

Giving patients more T cells would not bolster their immune system if the cancer is putting up a blockade or shield, Zou and others realized. This pushed researchers onto the right track: the discovery that major mechanisms, including CTLA4, PD-1/PD-L1, regulatory T cells and myeloid cells, were putting the brakes on the immune system.

Zou's lab was first to describe PD-L1 expression and function in the human cancer microenvironment and draining lymph nodes 16 years ago, proposing it as an important suppressive mechanism.

Why the immune system is important

Tapping into the immune system to treat cancer has three main advantages over other therapies:

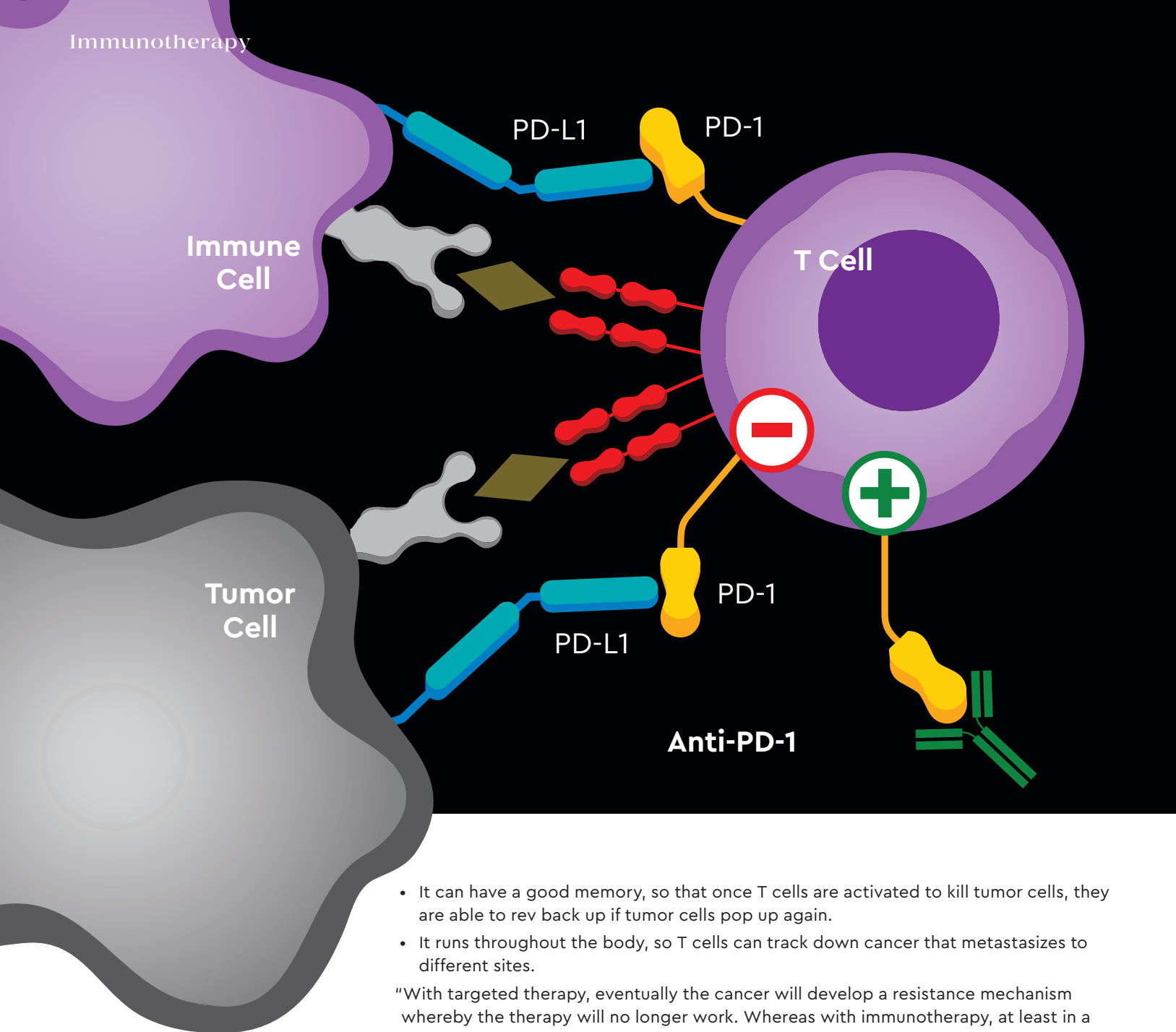
- It uses the patient's own body to target and kill the tumor cells, which limits the side effects.



Weiping Zou, M.D., Ph.D., speaks of the yin and yang of the immune system, referring to the balance of increasing patient survival and minimizing immune-related side effects.



Shirish Gadgil, MBBS, who sees lung cancer patients, examines Linda Gyles at her regularly scheduled follow-up appointment. Photo by Edda Pacifico



Above: In the tumor microenvironment, PD-L1 binds to PD-1, preventing immune cells from activating. By inhibiting PD-L1 and PD-1, the T cells are able to attack the tumor cell.

- It can have a good memory, so that once T cells are activated to kill tumor cells, they are able to rev back up if tumor cells pop up again.
- It runs throughout the body, so T cells can track down cancer that metastasizes to different sites.

"With targeted therapy, eventually the cancer will develop a resistance mechanism whereby the therapy will no longer work. Whereas with immunotherapy, at least in a minority of patients, once you've activated the immune system it may be able to keep the cancer under control for a long time, maybe even years," says Shirish Gadgil, MBBS, Mary Lou Kennedy Research Professor in Thoracic Oncology at the Rogel Cancer Center.

The challenge is what Zou calls the yin and yang of the immune system.

"It's the basic nature of the immune system. It's been designed to fight against invaders. When you have neoantigens in cancer, they have become invaders and the immune system wants to get rid of them," Zou says.

So it's key to mount a strong immune response quickly and efficiently, but then to shut it down. Too much immune activity and the body starts attacking itself, causing immune-related side effects.

Impacting patient care, outcomes

Some of the greatest success with immunotherapy has been seen in stage 4 melanoma and non-small cell lung cancer — two diseases that have historically had dismal outcomes with few options.

Lao recalls that just a decade ago, he had almost nothing to offer his stage 4 melanoma patients. Today, combination immunotherapy with ipilimumab and nivolumab has changed outcomes dramatically — from a median survival of six months to more than half of patients living at least five years.

In lung cancer, Gadgeel presented two-year outcomes at the 2019 American Society of Clinical Oncology annual meeting from the KEYNOTE-189 trial, which enrolled more than 600 patients with non-small cell lung cancer. Patients were randomized to pembrolizumab plus platinum-based chemotherapy or chemotherapy alone.

Patients who received chemotherapy and pembrolizumab had a median overall survival of 22 months, compared to 10.7 months for those who received chemotherapy alone. At two years, 45% of patients receiving combination therapy were alive, compared to 29% of patients on chemotherapy alone — a 16% improvement in overall survival.

"It's a huge difference, especially in lung cancer where until about two years ago the average range of survival was 10–12 months," Gadgeel says. He has patients who started on the trial in 2014 with stage 4 lung cancer, were treated for two years or less, and now are living with no evidence of disease.

"Admittedly, it's only a minority of patients. But to have even a minority of patients with no evidence of disease is extremely gratifying. We are very encouraged by these results but by no means satisfied," Gadgeel says.

Immunotherapy is also standard treatment in kidney and bladder cancer. It's been approved for Merkel cell carcinoma, squamous cell skin cancer and other cancers.

Long-term disease control potential for melanoma

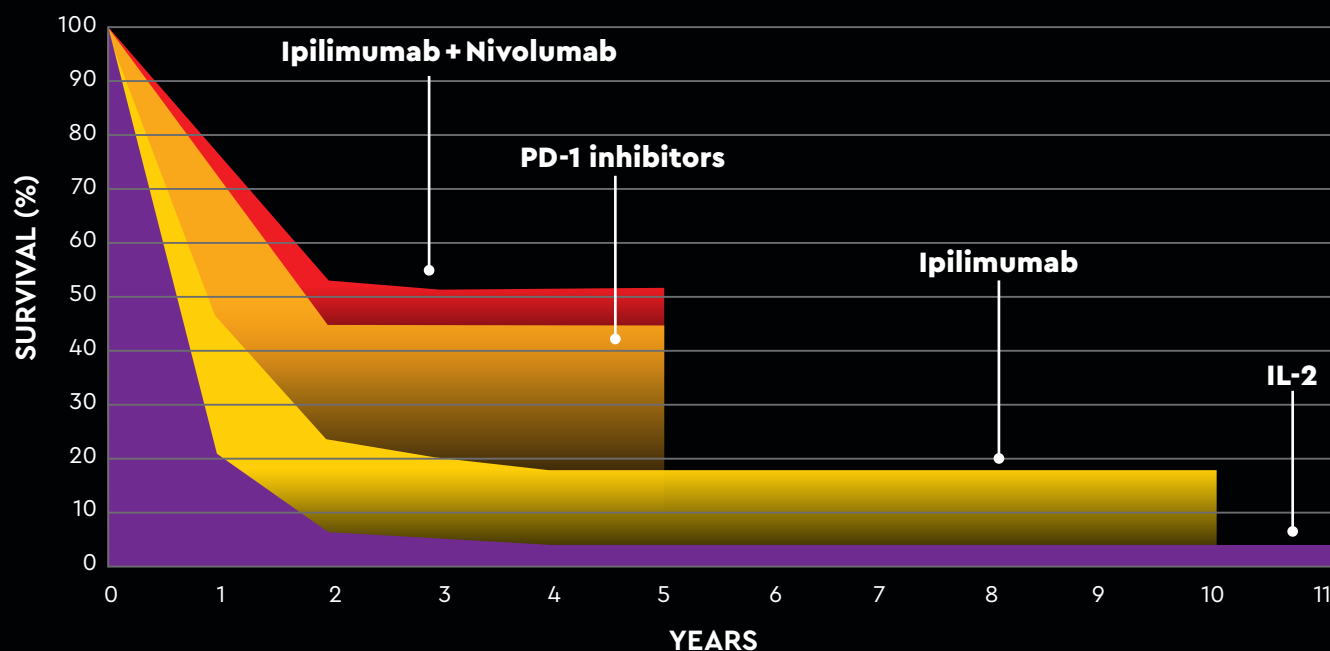


Image by Christopher Lao, M.D., MPH

Cellular therapy

In blood cancers, CAR T-cell therapies are a promising type of immunotherapy. The concept involves taking a patient's T cells and genetically engineering them to produce receptors on their surface called chimeric antigen receptors, or CARs. The engineered cells are infused into the patient's bloodstream, where they multiply. The receptors recognize cancer cells and kill them.

"CAR T-cell therapy has the potential to change the face of cancer therapy for years to come," says Gregory Yanik, M.D., clinical director of U-M's Pediatric Blood and Marrow Transplantation Program. "This allows us to turn patients' own cells into a powerful weapon to fight the disease."

Two CAR T-cell therapies have been approved by the Food and Drug Administration for acute lymphoblastic leukemia and diffuse large B-cell lymphoma. The Rogel Cancer Center was the first center in Michigan to offer all FDA-approved CAR T-cell therapies, and clinical researchers are investigating the therapy in additional cancer types.

Managing side effects

If increased survival is the yin of immunotherapy, the side effects are the yang. Triggering a strong immune response to kill the cancer also leads to immune-related side effects, including rashes, inflamed joints, thyroid or pituitary gland deficiencies, cardiomyopathy, enteritis or colitis, pneumonitis and nephritis.

At the Rogel Cancer Center, oncologists can leverage expertise across Michigan Medicine in fields such as rheumatology, gastroenterology, cardiology and endocrinology — which have previously had limited engagement with oncology — to manage these conditions.

"We're seeing that immunotherapy is a marathon, unlike a sprint with chemotherapy. With chemotherapy, you push as far as possible and then pull back when there are toxicities. With immunotherapy, if you reach toxicities, you need to hold off treatment and recover from them," says melanoma oncologist Leslie Fecher, M.D., associate professor of hematology/oncology at Michigan Medicine.

"For the most part these toxicities shouldn't be permanent. With effective management, we should get patients over these," she says.

Future opportunities

One of the biggest challenges in immunotherapy is that only about 30% of cancer patients overall respond to current checkpoint inhibitors. And among those who do, only a very small portion have sustained long-term responses that have people whispering a cure.

Rogel Cancer Center basic and clinical researchers are focused on three key questions:

- How can we make immunotherapy even more effective to generate more long-term responses?
- How can we make those who are not responding to immunotherapy sensitive to treatment?
- How can we control the immune-related side effects that arise from an active immune system, predicting which patients are at risk and learning how to manage them?

Clinical trials in melanoma, lung cancer and urologic cancers are looking at combining currently available therapies with other approved or new agents to try to expand the pool of responders. Researchers are also testing new immunotherapy agents to add to the arsenal of approved therapies.

"The uniqueness of U-M is that we not only have the capability of doing these early phase trials involving combinations of these agents with targeted therapy, radiation and cytotoxic chemotherapy," says Lao. "We also have amazing translational scientists working in the laboratory to develop new treatments and biomarkers to assess efficacy, which we can leverage in our trials. With this combination, the hope is we can advance the field and improve outcomes for patients."

On the laboratory side, Zou's lab has made fundamental discoveries explaining a suppressive mechanism of regulatory T cells and myeloid cells. In 2019, he published a paper in *Nature* describing a role for a little-known type of cell death called ferroptosis. When mice were given a checkpoint inhibitor drug in combination with a ferroptosis sensitizer, the impact on tumor growth was dramatically stronger than with either agent alone. *(Continued on page eight)*



A NEW APPROACH AGAINST GRAFT-VS.-HOST DISEASE

Rogel Cancer Center researchers move laboratory idea through to phase 3 clinical trial

Before checkpoint inhibitors, oncologists were successfully exploiting the immune system in another way: bone marrow transplant.

Here, the biggest issue is balancing the yin and yang of the immune system. That means firing it up enough to kill the cancer cells while limiting graft-vs.-host disease, a potentially deadly side effect rooted in a severely inflammatory environment.

Inflammation led to inspiration for Pavan Reddy, M.D. A 2011 paper suggested alpha-1-antitrypsin, a natural enzyme derived from human blood plasma, had anti-inflammatory effects.

"We asked a very obvious question: If it is really anti-inflammatory and it's a natural product made by every individual, could we use it to block the graft-vs.-host response?" says Reddy, division chief of hematology/oncology and deputy director of the Rogel Cancer Center.

His lab used alpha-1-antitrypsin in mice that received allogeneic bone marrow transplants and found the drug significantly reduced mortality from graft-vs.-host disease, compared to control mice who did not receive the drug.

In addition, they found alpha-1-antitrypsin reduced the number of inflammatory T-effector cells known to be present in graft-vs.-host disease. It also increased the number of T-regulatory cells, which play a positive role in immune responses.

They published this in 2012 in the *Proceedings of the National Academy of Sciences*. From there, they advanced the work into a phase 2 clinical trial using alpha-1-antitrypsin in patients with steroid refractory graft-vs.-host disease.

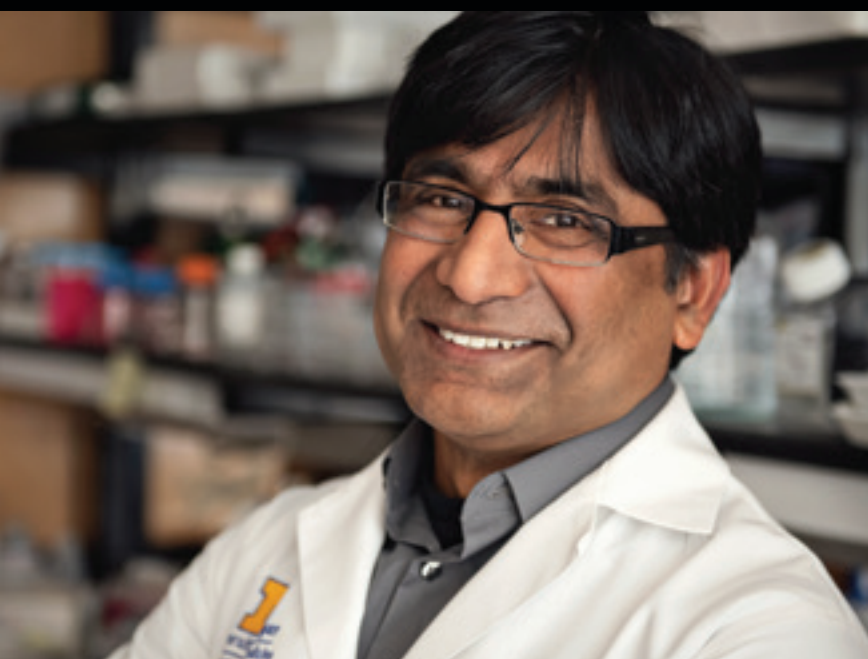
"These patients have a 75–80% mortality and pretty much nothing new being offered to them in terms of treatment options. We knew that if we could make a dent in this population, it would really be significant," Reddy says.

Results were promising. Of 40 patients evaluated, 26 responded to alpha-1-antitrypsin by day 28 — an overall response rate of 65%. By day 60, 73% of responders continued to see benefit without additional immunosuppression. Overall survival was 45% at six months, compared to 20–30% historically for this population. The study was published in 2018 in *Blood*.

"We're very pleased that the toxicity was really not observed at all. That plus the potential for efficacy makes this very exciting," Reddy says.

A phase 3 national clinical trial will open this year through the Clinical Trials Network, with backing from the National Cancer Institute and the National Heart, Lung and Blood Institute. The protocol will look at alpha-1-antitrypsin as an upfront therapy to see if adding it to steroids produces better response than steroids alone.

"There's an endless series of things that are unknown to work on. Hopefully one of them will make a big difference to people," Reddy says. "You've got to keep trying. It takes years and years and years to make a difference."



Pavan Reddy, M.D.

(Continued from page six)

"If ferroptosis is a critical pathway, we may be able to sensitize it to further stimulate immunotherapy or overcome resistance to immunotherapy," Zou says.

"We need to understand this better and work out different mechanisms."

THE MICHIGAN
RETROSPECTIVE
IMMUNOTHERAPY
EXPERIENCE IS A DATABASE
COLLECTING INFORMATION
ON PATIENTS TREATED
WITH IMMUNOTHERAPY,
WITH THE GOAL TO
UNDERSTAND WHO DOES
OR DOES NOT RESPOND
TO IMMUNOTHERAPY OR
DEVELOP TOXICITIES. IT
INCLUDES DATA FROM
MORE THAN 1,400 CANCER
PATIENTS TREATED AT THE
ROGEL CANCER CENTER.

Using new technology to enhance immune response

One potential way to make immunotherapy more impactful is to change the way it's delivered. James Moon, Ph.D., John G. Searle Associate Professor of Pharmaceutical Sciences at the College of Pharmacy, has developed a nanodisc to help deliver chemotherapy to cancer cells in a way that tricks the immune system. When combined with a checkpoint inhibitor, the nanodisc eliminated 85% of tumors in a mouse model of colon cancer.

In addition to producing a better immune response, new technologies seek to reduce the immune-related side effects.

"Checkpoint inhibition is amazing but it's very non-specific," says Clifford Cho,

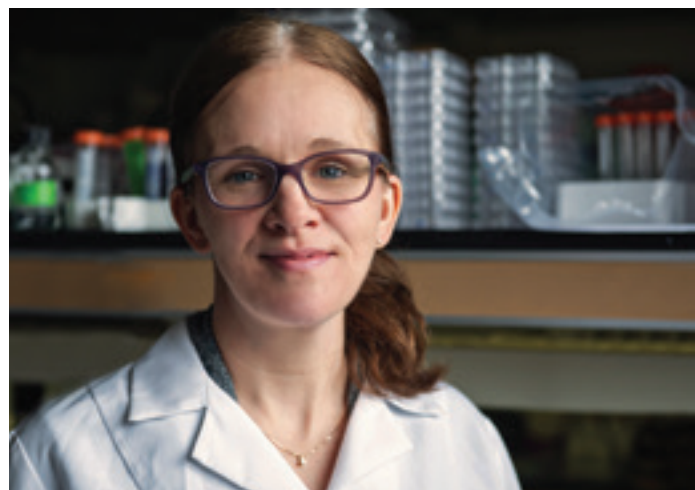
M.D., C. Gardner Child Professor of Surgery and chief of hepatopancreatobiliary and advanced gastrointestinal surgery at Michigan Medicine. "Generation 1 is checkpoint inhibition, but generation 2 is going to be targeting more specifically the part of the immune system that's going after the cancer."

Cho is exploring a new technique called histotripsy, which was developed by U-M engineers. It harnesses high-frequency sound waves and focuses them, like a magnifying glass focusing sunlight, into one small point. This causes rapid changes in pressure at the precise point and tears apart cell structures. Because the convergence point is so small and precise, it can be targeted very directly to a tumor without impacting surrounding normal tissue.

What Cho finds most exciting is that when the tumor cells are destroyed, they seem to release hidden proteins and peptides, which suddenly become exposed to the immune system.

"The histotripsy seems to make immunotherapy work even better," Cho says. "Histotripsy by itself is triggering an immune response, but when we add a checkpoint inhibitor, it's even more powerful. Our hope is that the immune reaction histotripsy is causing is revving up only an immune reaction to the cancer, not generally stimulating the immune system."

Cho received a grant from the Forbes Institute for Cancer Discovery at the Rogel Cancer Center to explore this idea further and move it toward translation. The Forbes Institute encourages scientists across the university to undertake high-risk, high-reward initiatives with the potential to drive new advances in cancer research. The intent is to fuel rapid development of innovative technology and new therapies.



Meredith Morgan, Ph.D.

Combining immunotherapy and radiation therapy

Laboratory work by Meredith Morgan, Ph.D., associate professor of radiation oncology at Michigan Medicine, is finding a synergy between radiation therapy and immunotherapy. Much like with histotripsy, radiation-induced cell damage releases hidden proteins that suddenly become visible to the immune system. In addition, the DNA damage that radiation causes can lead to DNA leaking from the cell's nucleus into the cytoplasm, where it is then recognized by the same immune system mechanisms that detect viral DNA following viral infections.

Morgan is using a DNA damage response inhibitor in combination with radiation. The idea: Trick the cell into thinking a virus is attacking. That then triggers the immune system, which would open the door for an immune checkpoint inhibitor to do its job.

"If we inhibit repair of radiation-induced damage, then in theory we should cause more of this damaged DNA to be leaked into the cytoplasm and therefore have greater immune response to tumor cells. The ultimate goal of this is to have a three-way therapy of immunotherapy, radiation and a DNA damage response inhibitor," Morgan says.

The approach has worked well in the lab, and plans for a clinical trial are underway.

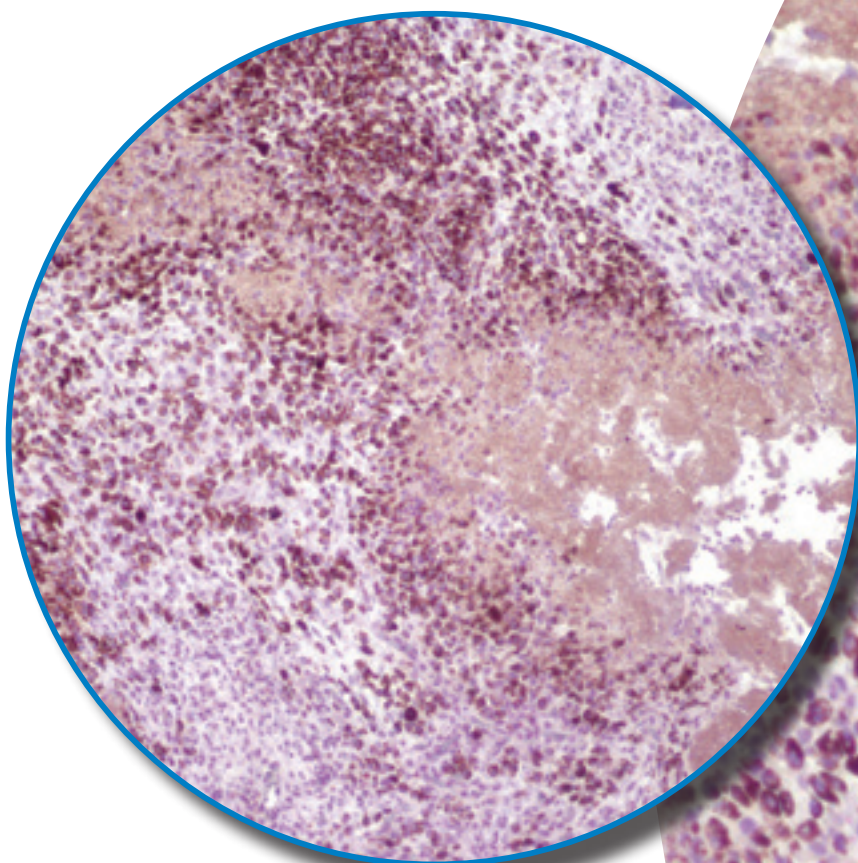
Tracking patients to understand outcomes

Recognizing the need to understand why only some of his patients respond to immunotherapy, Ajjai Alva, MBBS, M.S., began a database he calls the Michigan Retrospective Immunotherapy Experience. It includes data from more than 1,400 cancer patients treated with immunotherapy at the Rogel Cancer Center.

"While we are treating a lot of patients with immunotherapy in everyday practice, we are not really systemically collecting their data to see how are they doing. There are no great biomarkers for immunotherapy," says Alva, associate professor of hematology/oncology at Michigan Medicine.

A mouse melanoma tumor partially treated with histotripsy depicts dead tumor (brown area), viable cancer (light purple) and immune cells surrounding and attacking remaining cancer (dark purple).

Image by Clifford Cho, M.D.



The project has led to a number of grants, including a NIH U01 research grant for Alva and Lubomir Hadjiyski, Ph.D., professor of radiology at Michigan Medicine, to look at biomarkers in bladder cancer. Other researchers have also tapped the database to try to answer questions about who does or does not respond to immunotherapy or develop toxicities.

"We are still learning about immunotherapy — there is much unknown," Alva says. "But this is going to be a bigger and bigger part of oncology. We're all immunologists now in one way."



OUR OWN MEDICINE

What makes U-M one of the premier academic cancer drug development programs in the country?

BY IAN DEMSKY

WHEREVER SHE GOES, KELLY SEXTON'S MESSAGE IS THE SAME — WHETHER SHE'S MEETING WITH PHARMACEUTICAL EXECUTIVES IN THE BAY AREA, VENTURE CAPITALISTS IN NEW YORK OR OTHER POTENTIAL PARTNERS IN TURNING SCIENTIFIC ADVANCES FROM THE UNIVERSITY OF MICHIGAN INTO NEW MEDICINES FOR CANCER AND OTHER DISEASES.



Kelly Sexton, Ph.D.



Eric Fearon, M.D., Ph.D.

"When we meet with investors and executives, they're surprised to learn that we have the largest annual research volume of any public university in the country — over \$1.6 billion — and that we're No. 2 in the country for research funding from the National Institutes of Health," says Sexton, Ph.D., who heads the university's

office of technology transfer, which is responsible for the commercialization of research discoveries.

She also likes to point out that when it comes to drug discovery, an analysis by researchers at Yale and Washington University found U-M has discovered more novel molecular entities that have eventually led to compounds approved by the Food and Drug Administration than any other university or research institution in the world.

"At U-M, we bring the great breadth and depth of our expertise to bear on the fundamental genetic,

molecular and cellular mechanisms underlying human pathology," Sexton says. "And when you have a university as big as Michigan, additional layers of connection and support are critical — which is why we have programs to provide funding, mentorship and commercialization assistance."

That level of support has made a striking impression on ovarian cancer researcher Analisa DiFeo, Ph.D., who recently received an internal drug discovery grant to work with the U-M Center for Chemical Genomics to find inhibitors of a micro-RNA that is amplified in recurrent tumors.

"Having recently come from another institution, I can say the support for drug discovery at U-M is phenomenal," says DiFeo, associate professor of pathology and of obstetrics and gynecology at Michigan Medicine. "It's not like they just give you the money and say good luck. We just had the kick-off meeting for my project, and you could tell that everyone in the room was invested in its success."

The goals of the Rogel Cancer Center mirror those of the larger university, says Eric Fearon, M.D., Ph.D., Emanuel N. Maisel Professor of Oncology and director of the Rogel Cancer Center.

"The top goal is always to generate knowledge for the public good," says Fearon. "And while building knowledge about human health is tremendously valuable in itself, scholarly work also needs to have a tangible effect on people's lives."

A formidable foe

Developing new drugs is notoriously difficult and expensive — just 14% make it from early-stage clinical trials to approval by the FDA, according to an MIT study from 2018, the largest of its kind. And many thousands of efforts wash out before ever making it to an initial trial.

The success rate for oncology drugs in particular is even lower, the study found.

There are many reasons, including the nature of cancer itself — its stubborn intractability and the havoc wreaked in the body by the poisons used to curb it.

"Because of the sheer number of cells that you're trying to treat in a patient with advanced cancer and the high mutation rate, there's a strong likelihood there will be drug-resistant populations, even if you have a particularly good, targeted therapy approach," Fearon says.

This necessitates looking not only for new and better ways to shut down cancer's runaway growth and ability to spread, but also at multi-drug cocktails that aim to cut off every avenue by which cancer might retreat and retrench.

The Michigan difference

Despite the inherent challenges, U-M has developed one of the preeminent academic cancer drug development programs in the country, Fearon says.

"That's in terms of the quality and scope of the science, the number of targets that are being evaluated, the number of potentially interesting compounds that are being developed," he says. "In recent years, we've had nine compounds make it into initial human trials. That's a pretty enviable record for any academic institution."

At present, U-M Tech Transfer is tracking about 50 active anti-cancer drug-development projects that are closing in on a lead compound to advance to clinical trials, says Sexton.

"If we look at earlier-stage projects, it's in the hundreds," she says.

Cancer therapeutic technologies account for nearly 10% of Tech Transfer's entire portfolio. And out of these efforts, two to three new startups are formed annually to bring oncology discoveries to the clinic.

"It's a really exciting time for biomedical research and drug discovery at U-M," says Sexton, noting that \$500 million in new funds are supercharging investments in faculty recruitment, cutting-edge technologies and research programs. These include President Mark Schlissel's \$150 million Biosciences Initiative, a transformative \$150 million gift to the cancer center from Richard and Susan Rogel, \$38 million for the university's Precision Health research initiative, \$30 million to create the Chad Carr Pediatric Brain Tumor Center and a \$17.5 million gift to establish the Forbes Institute for Cancer Discovery within the cancer center.

Philanthropy is also helping to accelerate the development of new therapies. Tom McConnell, who sits on the Rogel Cancer Center's National Advisory Board, and his wife, Trish Turner McConnell, recently established a fund for early stage drug development efforts.

"The Rogel Cancer Center has the opportunity to fund deeply knowledgeable U-M cancer experts in early stage drug discovery," McConnell says. "These research scientists understand the etiology of the cancer disease process and have the expertise to develop novel compounds based on this understanding. Academic scientists at U-M may have more leeway to pursue innovative compounds targeting novel cancer disease pathways than traditional pharmaceutical developers who are constrained strictly by a profit motive."

Another factor in U-M's success, Sexton says, is Michigan Drug Discovery, an umbrella group that helps find, fund and mentor drug discovery projects across the breadth of campus. The Rogel Cancer Center is a major sponsor of the effort and is well-represented on its executive board.

The group awards pilot grants for use within the university's core laboratories for high-throughput screening, structural biology, pharmacokinetics and medicinal chemistry. To date, the effort has invested about \$2.3 million into more than 70 therapeutic projects — helping to secure more than \$17 million in additional support while advancing them from the bench toward the bedside.

Follow the science

Basic science researchers at the Rogel Cancer Center are divided into four programs, one of which is focused specifically on drug discovery. This developmental therapeutics program is co-led by Jolanta Grembecka, Ph.D., associate professor of pathology at Michigan Medicine, and Judith Sebolt-Leopold, Ph.D., research professor of radiology and pharmacology at Michigan Medicine. Both sit on the Michigan Drug Discovery executive committee.

Sebolt-Leopold spent two decades developing oncology drugs for Parke-Davis and Pfizer in the same scientific complex where her U-M lab now resides. Before she left the pharmaceutical industry, she headed up a department of more than 100 scientists involved in early stage drug discovery across many therapeutic areas.

"Greater than 80% of the members of the Rogel Cancer Center's developmental therapeutics

THE UNIVERSITY OF MICHIGAN IS A RESEARCH POWERHOUSE

\$1.62 billion

the **largest annual research volume** of any public university in the country

No. 2 in the country

for research funding from the
National Institutes of Health

U-M has discovered
**more novel
molecular entities**
that have eventually led to compounds
approved by the Food and Drug
Administration than any other university
or research institution in the world,
according to a study in *Drug
Discovery Today*.

program have filed patents or have intellectual property disclosures that have contributed to our portfolio," Sebolt-Leopold says. "To me, that's a great measure of how successful and active our program has been."


Sebolt-Leopold can count herself among that number. In addition to her research program at U-M, she co-founded Mekanistic Therapeutics, a startup company dedicated to the rational design and development of kinase inhibitors that selectively inhibit multiple oncogenic pathways.

Together with Christopher Whitehead, Ph.D., also a former member of Pfizer's MEK inhibitor research team, Sebolt-Leopold developed a lead compound — MTX-211 — which represents a first-in-class molecule that selectively and potently inhibits EGFR and PI3K, two critical oncogenic kinases known to drive

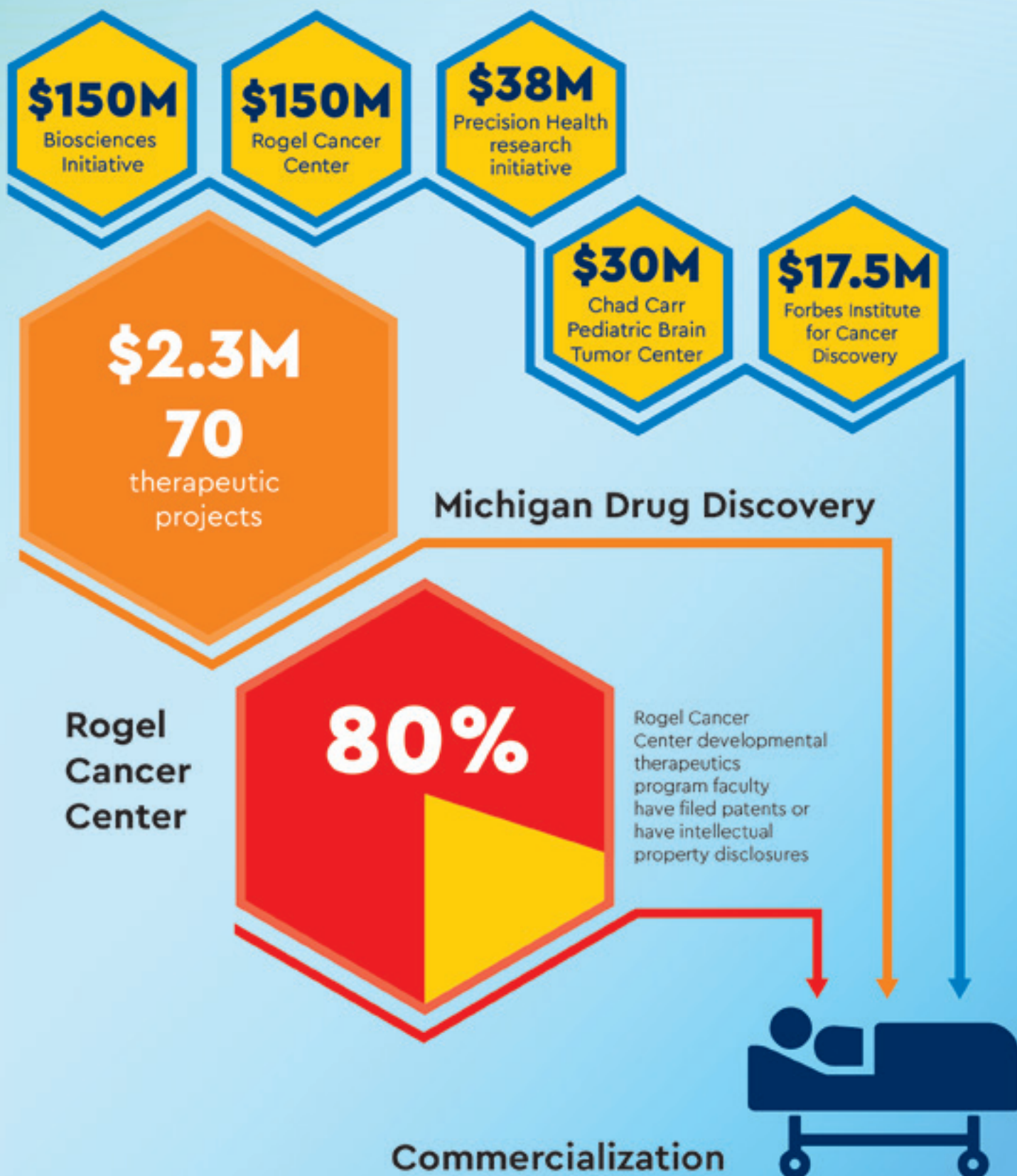
progression in a number of tumor types, including squamous carcinomas and colorectal cancer.

"It's effectively a combination approach in a single molecule," she says, adding that the company expects to file its application with the FDA to launch clinical trials in 2020.

Meanwhile, she stresses how proud she is of the therapeutics program as a whole.

"We have a nice balance of projects at every stage of the drug discovery continuum," Sebolt-Leopold says. "And we have great diversity in the approaches our faculty are taking. There is no one right way. You have to follow the science with the ultimate goal of matching the right drug to the right patient." 

Funding the Future of Discovery across U-M





DRUG DISCOVERY SPOTLIGHT

With dozens of U-M projects across every stage of the drug discovery pipeline, here's a look at how several Rogel Cancer Center researchers aim to turn insights made at the lab bench into tomorrow's treatments.

Lasting tumor regression in leukemia and lymphoma mouse models

For decades, a transcription factor known as STAT3 has been a major therapeutic target in cancer. But STAT3 has largely been considered undruggable due to the difficulty of developing compounds to effectively inhibit its activity.

Researchers at the Rogel Cancer Center have taken a promising new approach to targeting STAT3 — developing a small-molecule compound that harnesses the power of a natural cellular “cleanup” system to get rid of it entirely, rather than traditional methods that have tried to block its action.

The U-M compound was able to achieve a long-lasting and nearly complete elimination of tumors in mouse models of leukemia and lymphoma, the authors reported in *Cancer Cell*.

“STAT3 plays a major role in almost every aspect of human cancer,” says study senior author Shaomeng Wang, Ph.D., Warner-Lambert / Parke-Davis

Professor of Medicine at the U-M Medical

School and professor of medicinal chemistry at the College of Pharmacy. “It also has been implicated in autoimmune and inflammatory diseases. So, there's a lot of therapeutic potential if one can target STAT3 successfully.”

Working with Oncopia Therapeutics, a U-M start-up company co-founded by Wang, the research team is completing studies required for filing an investigational new drug application with the FDA, which is required to initiate human clinical trials.

**U-M-developed
STAT3 degrader
achieves long-lasting
elimination of tumors
in mouse models**

U-M-developed drug for acute leukemia enters clinical trials

Protein-protein interactions, such as those that occur between menin and MLL fusion proteins in a rare type of acute leukemia, had long been considered undruggable. And current treatments are not very effective, with just over a third of patients surviving five years.

Rogel Cancer Center researchers Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D., developed the first small molecule inhibitors of the interaction between menin and MLL.

“The MLL-menin interaction is a good drug target because it's the primary driver of this type of leukemia,” says Grembecka, associate professor of pathology at Michigan Medicine. “By blocking this interaction, it's very likely to stop the cancer.”

The interaction is found in about 10% of adult acute leukemia cases and 70% of infant cases.

To advance their research findings into clinical trials, the university partnered with Kura Oncology. Joint efforts led to the development of a clinical candidate compound, KO-539, which received approval from the FDA in March 2019 for a phase 1 trial. The trial, in patients with relapsed acute myeloid leukemia, launched in September.

Meanwhile, Grembecka and Cierpicki, associate professor of pathology at Michigan Medicine, have been collaborating with other U-M researchers to assess the activity of their menin-MLL inhibitors in prostate cancer, Ewing sarcoma and melanoma, which feature the same interaction.



**Tomasz Cierpicki, Ph.D.
and Jolanta Grembecka, Ph.D.**

KO-539
received approval
from the FDA in March
2019 for a phase 1
trial for patients with
relapsed acute myeloid
leukemia

Machine learning: A United Nations approach to drug discovery

On one side of the equation, there are some 100,000 human proteins or protein-protein interactions that are potentially druggable, says medicinal chemist Nouri Neamati, Ph.D., John G. Searle Professor of Medicinal Chemistry at the College of Pharmacy.

On the other side, the number of chemicals that could potentially serve as drugs: a one followed by dozens of zeroes.

"You'd want to mathematically match the right chemical with the right target, right?" he says. "But, no — it's impossible, because for any given target you have billions and billions of possibilities."

Neamati's approach is to let smart computer algorithms do the heavy lifting — drawing on the same machine learning techniques used by services like Netflix and YouTube to personalize recommendations based on what other users with similar tastes have watched.

"Machine learning is used in practically every area of life, but in terms of drug discovery it's fairly new," says Neamati.

Neamati has developed a database containing 10 million compounds, which he's grouped together into different clusters. He keeps 40,000 reference samples in 11 freezers in his lab.

"We call them the United Nations of compounds because of the way the United Nations works: you have one person representing an entire country," he says. "So we have one compound from each cluster of compounds — sulfonamides, benzamides — representing all the rest."

When a promising result is found, a cluster can be explored more deeply. In a recent interview, Neamati pointed to two ongoing projects that have emerged using the technique.

While antioxidants may be popular dietary supplements, recent research in lung cancer patients has shown they may actually make things worse. Neamati's group has found promise in an opposite approach.

"Normal cells can cope with adding pro-oxidants, but a cancer cell is already so stressed, when you add the pro-oxidants the cells just crash and burn," he says, expressing optimism about preclinical studies underway in a pancreatic cancer model.

Another of his lab's projects targets a protein that is responsible for correctly folding thousands of other proteins so they can function correctly. As cancer cells replicate, this protein is essential to maintaining a semblance of order inside the rapidly dividing cells, especially in brain cancer.

"Imagine you go into a clothing store and instead of being neat and orderly on the shelf, the clothing is just piling up everywhere in a big mess," Neamati says. "If we inhibit this key protein, the cancer cells die because they can't cope with so much unfolded protein everywhere."



Nouri Neamati, Ph.D.

A database of
10M
compounds

40K
reference
samples



CANCER BYTES

How U-M researchers are using big data to transform cancer care

BY IAN DEMSKY

THE OLDEST KNOWN MEDICAL TEXT ON CANCER DATES BACK MORE THAN 3,500 YEARS TO AN EGYPTIAN TREATISE ON SURGICAL CASES. ACCORDING TO THE UNKNOWN PHYSICIAN, POSSIBLY THE LEGENDARY IMHOTEP, A PATIENT MAY PRESENT WITH BULGING TUMORS OF THE BREAST. IF THESE ARE HARD AND COOL TO THE TOUCH, THE TEXTURE OF "GREEN HEMAT FRUIT," THEN THE WORST CAN BE EXPECTED.

"THERE IS NO TREATMENT," THE ANCIENT AUTHOR NOTES.

The idea of individual doctors examining, diagnosing and tending to individual patients is as old as human history. In recent years, however, something new and exciting has been happening — physicians and researchers, including those at the University of Michigan Rogel Cancer Center, are tapping into the wealth of previously inaccessible information in patients' individual cancers and bringing that data together to help improve care for millions. The umbrella term from this work has come to be known as big data.

"Cancer researchers have actually been using big data and cutting-edge computational methods for quite some time, relative to other chronic diseases," says Bhramar Mukherjee, Ph.D., chair and John D. Kalbfleisch Collegiate Professor of Biostatistics and associate director for quantitative data sciences at the Rogel Cancer Center. "That's because there's so much meaningful data to work with — tumor sequence data, germline genetic data, and all of the -omics: like gene expression, methylation, proteomics, metabolomics and studies of the microbiome. We are rapidly entering the age of omni-omics."

One of U-M's strengths, she notes, lies in the breadth and depth of expertise across campus, which gives rise to powerful collaborations between data scientists, those studying cancer biology and genetics in the laboratory, and clinicians with firsthand experience caring for patients.

A risky business

Not everyone who smokes cigarettes gets cancer. Neither are genetics a clear predictor — 8 out of 10 women who develop breast cancer have no family history of the disease.

Whether an individual develops cancer depends on a complex interplay between underlying genetic factors, environmental factors like exposure to toxins, and lifestyle choices, such as diet, smoking, alcohol use, exercise and tanning.

Mukherjee and her team have a goal of enabling real-time precision prevention in cancer. They are using data drawn from the electronic health records of more than 65,000 U-M patients who have opted into a study called the Michigan Genomics Initiative. The researchers want to better understand not simply which genetic mutations give rise to specific cancers, but also what other medical conditions and test results might serve as early warning signs.

Access to patients' entire health records has provided a rich history spanning years, Mukherjee says, with an average of 27 doctor visits and 31 diagnostic codes associated with each patient.

"We're looking for cases where we can agnostically find a disease, or a cluster or pattern of diseases, that arise long before an actual cancer diagnosis," Mukherjee says.

"This is particularly important for cancers for which we do not have good screening tools — like pancreatic cancer and ovarian cancer."

Ultimately, the goal is to go even further, pairing data from patients' medical records and blood samples with a broad spectrum of information to paint a unique portrait of the factors that give rise to disease: tumor data, dental records, neighborhood information, air quality data, prescription claims, death records and so on.

A central pillar of the group's current analyses is a risk-prediction tool known as a polygenic risk score. As the name implies, it's made by aggregating small contributions to disease risk from individual genetic flaws into an easier-to-work-with grouping that represents a family of mutations.

"The idea is to increase the predictive power of our studies by collapsing multiple risk variants into a single biomarker," says Lars Fritsche, Ph.D., an assistant research scientist in Mukherjee's group, who has led much of the research.

The second pillar is the wealth of unique patient data from the Michigan Genomics Initiative, which launched in 2012.

In 2019, Mukherjee's research team published a study in *PLOS Genetics* with two major findings. Using skin cancer as a test case, they found that polygenic risk scores constructed from large, public datasets accurately lined up with actual patient data — that is, patients with a high genetic risk score for skin cancer tended also to have been diagnosed with skin cancer.

But the more interesting finding was that the data also surfaced other conditions and traits among these patients. For example, the data showed actinic keratosis (scaly skin growths caused by sun damage and known to be pre-cancers) showing up in patients who were later diagnosed with skin cancer. The data was able to map how early the keratosis tends to show up before skin cancer is found.



Bhramar Mukherjee, Ph.D.

By showing that the approach can accurately find known cancer precursors, the researchers believe in the future it will help uncover associations that would otherwise go overlooked.

More broadly, the researchers anticipate polygenic risk scores may soon start to be used in the clinic, particularly for monitoring patients at highest risk.

"The question is, can we put some patients on high alert, maybe introduce screening at an earlier time or recommend a behavioral change that can have the biggest impact?" Mukherjee says.

Re-modeling prostate cancer

For years, clinicians have relied on a standard set of tools to figure out which prostate cancer cases are likely to be aggressive and spread: prostate-specific antigen, or PSA, level, tumor stage and Gleason score, a grading system based on how biopsied cells look under the microscope.

Daniel Spratt, M.D., Laurie Snow Research Professor of Radiation Oncology at Michigan Medicine, is part of a team of researchers who want to improve predictions by incorporating patients' genomic data into the equation.

They developed a clinical genomic model that adds in data from a commercial, 22-gene test called Decipher. The model significantly improved upon the predictive power of the standard models used to classify men into a six-tiered system of low, intermediate and high risk, according to findings that the research team published in the *Journal of Clinical Oncology*.

"We found it reclassified about two-thirds of men," says Spratt, the study's lead author. "That tells me that without genomics, we're wrong fairly often about how aggressive a patient's disease is going to be. And that means there are a significant number of patients we can spare the cost and side effects of treatment."

Michigan Genomics Initiative

65,000

patients

D

B

tumor data | dental records | neighborhood information

EACH PATIENT:

~27 visits
~31

diagnostic
codes

The group's findings showed about half of patients classified with favorable, intermediate risk under National Comprehensive Cancer Network guidelines would be reclassified as low risk by the genomics model. Therefore, the model could increase the confidence of doctors and patients for pursuing active surveillance rather than immediately jumping to surgery or hormone therapy. Meanwhile, about 15% of low risk patients were actually at higher risk when genomics were factored in.

The study also identified a new cohort of patients at very high risk for metastasis who would likely benefit from more aggressive treatments and who would be good candidates for experimental clinical trials.

"Prostate cancer is being left behind in the era of precision medicine," Spratt says. "Adding genomics to our clinical toolkit could radically change the way we perceive and treat localized prostate cancer."



Daniel Spratt, M.D., attends a tumor board discussion with other U-M cancer specialists.

10 years | **2.5** petabytes of data
33 cancer types | **11,000** tumors
27 papers published in

DATA

n | air quality data | prescription claims | death records

Working closely with Todd Morgan, M.D., chief of urologic oncology at Michigan Medicine, Spratt is undertaking new research to further validate the genomics model and develop the data needed to recommend its use as a new standard for clinical practice.

Mapping the future of cancer research

The goal of The Cancer Genome Atlas was simple: to create a new, more comprehensive understanding of how, where and why cancer arises.

The decade-long project combined the efforts of researchers across the globe, assembling and analyzing 2.5 petabytes of data spanning 33 cancer types and 11,000 tumors — enough data to fill up 2.5 million iPhones. Its final report, the Pan-Cancer Atlas, was published in 27 papers across the Cell Press family of journals in 2018.

Thomas Giordano, M.D., Ph.D., Henry Clay Bryant Professor of Pathology at Michigan Medicine, served on the Pan-Cancer Atlas steering committee and co-led TCGA projects on thyroid and adrenal cancer.

U-M researchers also contributed tumor samples and led several other projects, including in esophageal cancer, and head and neck squamous cell carcinoma.

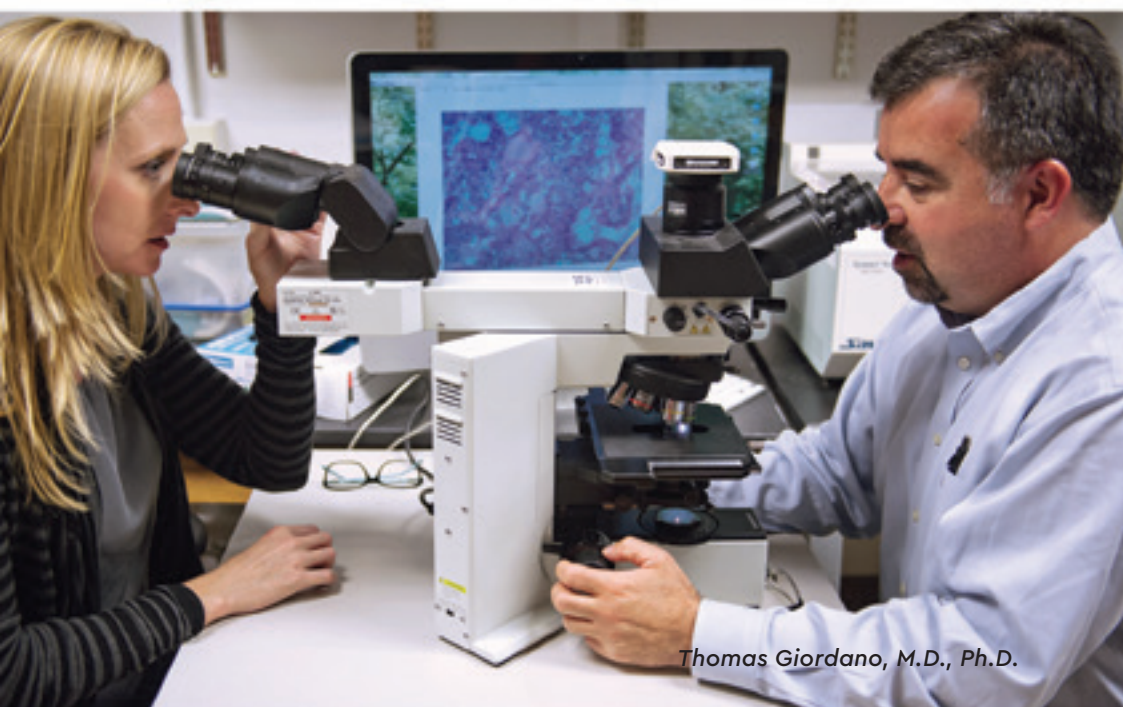
"Overall, we learned a great deal about the molecular basis of cancer and discovered new mutations, which have helped improve molecular diagnostics," Giordano says. "We learned a lot about the consequences of specific mutations and how they drive the biology of tumors. Nearly all of the projects identified three to five molecular subgroups of cancer, some of which had not been previously identified."

In papillary thyroid cancer, for example, two mutations involving proteins in the same signaling pathway were previously believed to be essentially functionally equivalent. But the research data revealed different signaling properties, which has led to changes in how these tumors are classified, and thus improved the care and treatment patients receive, Giordano says.

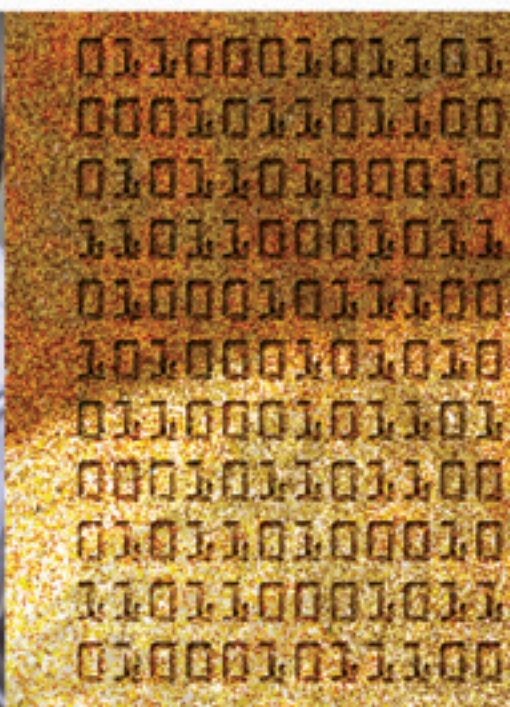
"Today, when researchers study thyroid cancer — or many other types of cancer — they can compare their results to the atlas and have a robust dataset for comparison," he says.

A good example can be seen in the work of ovarian cancer researcher Analisa DiFeo, Ph.D., associate professor of pathology and obstetrics and gynecology at Michigan Medicine.

She's trying to develop compounds to inhibit a specific microRNA that's enriched in recurrent ovarian cancer tumors — with the idea that blocking it may be able to help prevent the cancer's return.



Thomas Giordano, M.D., Ph.D.




In the atlas, DiFeo can see that patients with amplification of this same microRNA across cancer types have significantly worse outcomes.

"So the hope is that if we can find a drug to target this microRNA, it won't only apply to ovarian cancer, but could potentially apply to many other types of cancer," she says.

David G. Beer, Ph.D., professor emeritus of surgery at Michigan Medicine, found a promoter duplication in a protective enzyme in the genome of Caucasians that is associated with reduced expression and may help to explain why they have higher rates of the most common type of esophageal cancer.

"Risk factors like obesity and reflux are happening at the same rate for African Americans and Caucasians, but African Americans are not getting cancer," he says. "It's not just the presence of the genomic duplication, but also these other factors contributing to the damage of the esophagus that contribute to increased risk of developing cancer."

Beer and his colleague Laura Kresty, Ph.D., associate professor of thoracic surgery at Michigan Medicine, have seen promising initial results from research into whether cranberry-derived flavonoids, a type of phytonutrient, could help reduce levels of DNA damage caused by reflux.

"Fundamentally, this data is already changing how patients are treated," Giordano says. "And it's an amazing resource to build upon in the years to come." 



Building a Better Mouse Map

Just as The Cancer Genome Atlas has molecularly characterized thousands of human tumors across many cancer types, Kathleen Cho, M.D., is among a group of U-M faculty working to create its equivalent in mice. A Mouse Cancer Genome Atlas, if you will.

"Those of us who work in the field have recognized the tremendous value that the human genome cancer atlas, the TCGA, has provided," says Cho, Peter A. Ward Professor of Pathology, professor of internal medicine and head of gynecologic pathology at Michigan Medicine. "At U-M, we have a lot of strength in developing genetically engineered mouse models of specific cancer types. The question is, how well do the mouse tumors recapitulate their human counterparts? Or, among several leading mouse models, how do we know which one is best?"

In trying to recreate human disease as closely as possible, scientists consider several factors in engineering genetic defects into mice: Do the cancers occur in the right place? Do they look like their human counterparts under the microscope? Do they distribute themselves across the body in the same way when they metastasize? Does variation among individual mice follow a similar pattern to human patients?

"And if we were to look at the DNA, the RNA and the proteins in the mouse tumors, do we see the same kinds of alterations at the molecular level that we see in human tumors as described by the TCGA?" Cho says.

The ultimate goal, she says, would be to develop a new resource for cancer researchers around the globe.

"In my field, for example, there have been several different models developed for high-grade serous carcinoma, the most common form of ovarian cancer," Cho says. "And, of course each group thinks their model is the best one. But if you wanted to move forward with testing a novel therapy or prevention strategy, ideally you'd like to choose the model that has been proven to be the best mimic of its human counterpart."

"It's a lot less expensive to do preclinical studies in animal models than to do human trials, but they do require resources and are time-consuming — so you don't want to be putting your eggs in the wrong basket," she continues. "Ultimately, an inferior model could lead to a sub-optimally designed human clinical trial."



Kathleen Cho, M.D.

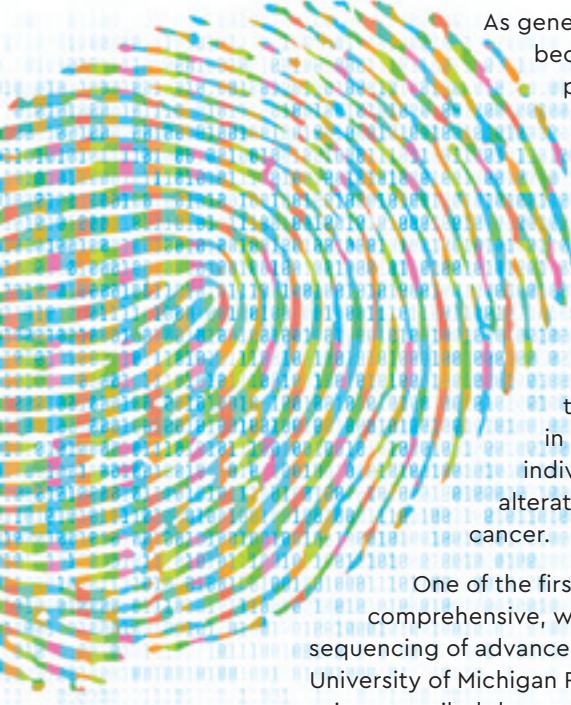


GENETIC DATA IMPACTS CLINICAL CARE

An increased demand for genetic testing engages patients and family members

BY BETH UZNIS JOHNSON

CANCER BY DEFINITION IS A GENETIC DISEASE CAUSED BY ALTERATIONS IN THE GENETIC CODE THAT OCCUR IN INDIVIDUAL CELLS. MOST CANCERS DEVELOP WHEN THESE ALTERATIONS TRANSPIRE AT RANDOM IN A PERSON'S LIFE, WHILE OTHERS ARE FACILITATED FROM AN INHERITED COPY OF A PARTICULAR GENE THAT CAUSES CELLS TO BECOME CANCEROUS MORE EASILY.



As genetic testing of tumor tissue becomes more common among patients recently diagnosed with cancer and moves closer to standard of care for identifying certain types of alterations, these genetic data are being systematically collected and analyzed by researchers. In addition to testing genes in tumors, there is increased interest in understanding whether individuals have hereditary alterations in genes that promote cancer.

One of the first cancer centers to perform comprehensive, whole exome clinical sequencing of advanced cancer tumors, the University of Michigan Rogel Cancer Center is now using compiled data to shed light on what genetic alterations occur in the tumor relative to the patient's normal — germline — genome.

These rich collections of genetic data are allowing researchers to develop new targeted therapies, match patients to clinical trials based on genetic alterations, better manage patients and at-risk family members, and take steps to utilize precision oncology approaches earlier in the process, before tumors have evolved and developed resistance mechanisms making them more challenging to treat.

Understanding molecular drivers of advanced cancer

In a 2017 paper in *Nature*, researchers at the Rogel Cancer Center found a significant increase in the number and type of genetic mutations between metastatic cancer and primary cancer. Nearly every case of metastatic cancer in 500 adult patients with solid tumors had more mutations.

Sequencing RNA in addition to DNA revealed a host of molecular factors that play a role in the tumor microenvironment, fostering and allowing the cancer to continue to grow, spread or evade treatment. Researchers found RNA sequencing shed light on the underlying mechanisms that either turn on cancer-causing genes or turn off the genes meant to stop cancer. This could help identify potential targets for treatment.

As part of the Michigan Oncology Sequencing Program, known as Mi-ONCOSEQ, patients undergo a CT-guided biopsy of their metastatic tumors and provide blood samples to test their normal DNA, the germline. Whole exome sequencing is carried out on all expressed genes — both DNA and RNA — and compared with germline sequencing. Since its inception nearly a decade ago, more than 3,500 patients with advanced cancer at the Rogel Cancer Center have elected to have whole or targeted exome sequencing.

A computational approach is used to analyze the data and create molecular reports, which are discussed at a precision medicine tumor board that includes a team of oncologists, genetics specialists, pathologists, bioinformatics specialists and genetic counselors, among others. Results are shared with patients, who also receive genetic counseling.

"The focus is on discovering key targets or biomarkers in individual patients that can be developed into diagnostic and prognostic tests for patients, as well as understanding the biology of an individual patient's cancer," says Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology. "By understanding what's driving the tumor from a molecular basis and how they mechanistically work, we can develop therapies or match patients to the right therapies."

Another striking finding in the *Nature* paper was that 12% of the metastatic cancer patients harbored an inherited mutation. About three-quarters were related to the process of DNA repair, which several existing therapies are designed to target.

As is the case in cancer discovery, Chinnaiyan's vision for Mi-ONCOSEQ and initial study results led scientists down many paths for further research — some anticipated, others not — but all needing exploration.

Using genetics data in the clinic

Fast forward to 2020 where Elena Stoffel, M.D., MPH, directs the Cancer Genetics Clinic and Sofia D. Merajver, M.D., Ph.D., directs the Breast and Ovarian Cancer Risk Evaluation Program at the Rogel Cancer Center. The demand for genetic testing is increasing tremendously. The information is instrumental in both determining treatment algorithms for patients with cancer, but also risk-stratifying relatives and improving the ability to prevent cancers in at-risk family members.

Stoffel's and Merajver's research interests involve the longitudinal management of people with genetic predisposition to cancer, specifically hereditary gastrointestinal cancers (Stoffel) and breast cancer (Merajver). Lynch Syndrome and hereditary breast and ovarian cancer are defined as high-penetrance hereditary cancer syndromes. Both impact approximately 1 in 300 people.

Stoffel also studies the incidence of colorectal cancers in young people, those diagnosed before the age of 50. In a 2019 paper in *Gastroenterology*, findings indicated that 20% of young people

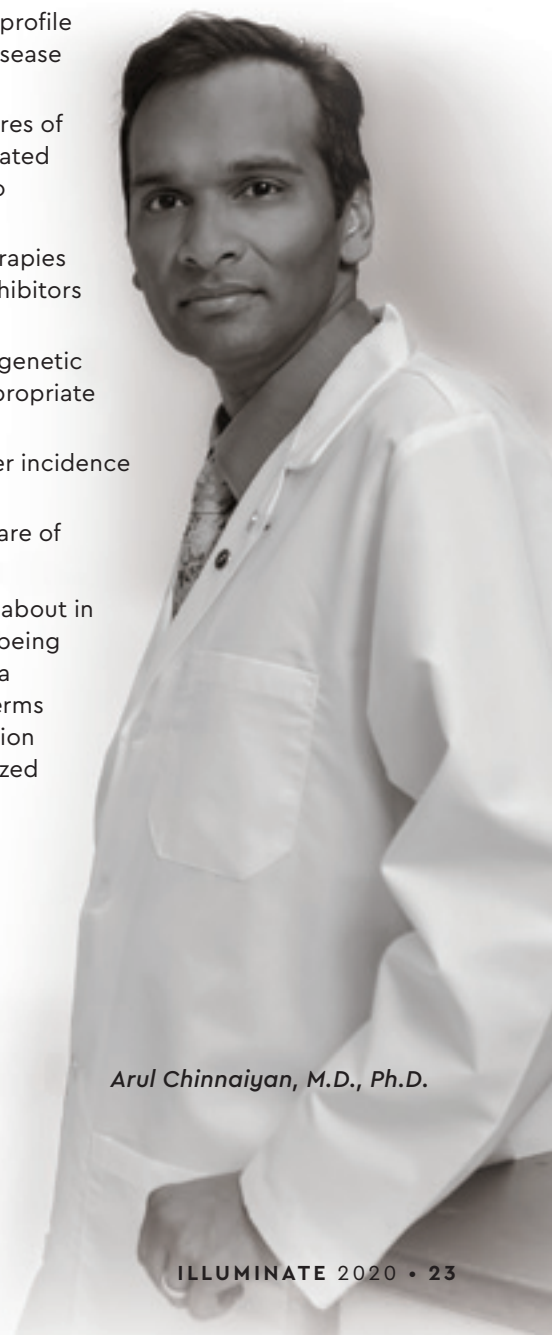
diagnosed with colorectal cancer have an inherited genetic abnormality that predisposes them to its development.

"Our study suggests that even in the absence of a family history of cancer, the prevalence of inherited factors is so high in young colorectal cancer patients that it makes sense to test everyone, as these heritable alterations can impact their care as well as the care of their family members," Stoffel says.

Because of their roles in the management of patients at hereditary risk for cancer, Stoffel and Merajver collaborate broadly with researchers across the Rogel Cancer Center with expertise in cancer genetics, including those working to:

- identify biomarkers and other drivers of cancer tumors
- understand the molecular profile of cancer tumors across disease types
- pinpoint particular signatures of tumors that may be associated with different responses to different therapies
- develop new targeted therapies like immune checkpoint inhibitors and PARP inhibitors
- identify patients with pre-genetic syndromes and ensure appropriate follow up
- explain disparities in cancer incidence and prognosis
- manage the longitudinal care of cancer survivors

What Stoffel is most excited about in her work is that insights are being developed to move beyond a one-size-fits-all strategy in terms of cancer screening, prevention and treatment to a personalized approach for each patient.



Arul Chinnaiyan, M.D., Ph.D.

**A NEW TYPE OF
CLINICAL TRIALS,
KNOWN AS BASKET
TRIALS, IS BASED
ON PATIENTS'
INDIVIDUAL
MOLECULAR
ALTERATIONS,
RATHER THAN
CANCER TYPE.**

"Through the molecular profiling being done at the Rogel Cancer Center, we're identifying particular signatures of tumors," Stoffel says. "Understanding these basic molecular mechanisms that underlie different cancer types, we now know some genes overlap cancer types. These breakthroughs are allowing us to move towards an approach where we tailor our treatments to the underlying processes rather than just the same old way of treating the cancer type."

In the Merajver lab, researchers are developing new therapies for the most aggressive cancers that arise in hereditary breast and ovarian cancer syndromes, as well as discovering the alterations in tumors most likely to respond to certain drugs, thus paving the way for true precision oncology. Both clinics work in teams of physicians and dedicated genetic counselors to provide comprehensive care to their patients and the family members.

Of the hundreds of genes in cancer, there are now several dozen that have clinical implication for management and prevention of cancer. Between Stoffel's work in the Cancer Genetics Clinic and Merajver's work in the Breast and Ovarian Risk Evaluation Clinic, more than 3,000 patients are referred each year for clinical genetic testing.

Making a difference worldwide for patients with rare diseases

With progress being made to understand the most common, highly penetrant and well-defined syndromes with genetic predispositions, what about those patients with more rare cancer syndromes?

Tobias Else, M.D., explains how collaboration — across the U.S. and around the world — to collect genetic data has made a difference in the lives of patients and family members with very rare endocrine tumors.

Else, associate professor of internal medicine at Michigan Medicine, runs a research laboratory closely tied to his work with patients in two clinics: Stoffel's cancer genetics clinic and the Endocrine Oncology Clinic, led by Gary Hammer, M.D., Ph.D., Millie Schembechler Professor of Adrenal Cancer.

For the past several years, Else has managed the Michigan Endocrine Cancer Repository, which is the world's most comprehensive genomic and genetic analysis of adrenal cancer. The adrenal researchers at U-M also started the American-Australian-Asian Adrenal Alliance, called A5, which now has around

30 institutions worldwide that contribute data. A5 has led to clues about rare adrenal and endocrine cancers that have directly informed Else's work with patients in the clinic.

The rarity of endocrine diseases inherently challenges the ability to do impactful research, publish findings with broad application and develop guidelines to provide evidence-based clinical care. Else outlined these issues in a letter in *Hormones and Cancer* in 2019.

The A5 consortium is pivotal to uncover the molecular mechanisms of tumor growth and novel insights that will lead to the next generation of adrenal cancer therapies. It allows researchers globally to collaborate, identify biomarkers and genetic markers of adrenal cancer, study the genetic syndromes for these tumors, and accelerate discovery by enabling large-scale, long-term longitudinal studies of patients.



Sofia D. Merajver, M.D., Ph.D.



Elena Stoffel, M.D., MPH

Else leads the von Hippel Lindau Comprehensive Clinical Care Center and follows 50–60 patients and at-risk family members with von Hippel-Lindau disease, a hereditary genetic condition also known as VHL. He collaborates with specialists throughout the Rogel Cancer Center and Michigan Medicine to guide the surveillance and decision-making process for this rare genetic syndrome, which can cause tumors of the kidney, adrenal glands, pancreas, and blood vessel tumors of the brain and eyes.

"Building long-term relationships with patients and families sparked my interest in endocrinology and cancer genetics," Else says, adding that patients he first encountered as kids are now off to college. "You get to know them well, generation after generation."

Else helps coordinate annual visits for VHL patients, where they have blood drawn for analysis and an MRI of the brain, spine and abdomen to screen for tumors. Patients also have an eye exam by an ophthalmologist and receive genetic counseling. By coordinating annual care, Else aims to make VHL prevention and screening a minimal part of patients' everyday lives.

Communicating the value of testing and sharing results



Steven J. Katz, M.D., MPH

Cancer registries that include genetic and other data are unique treasures in the United States, according to Steven J. Katz, M.D., MPH, professor of medicine and health management and policy at the University of Michigan. Much of his work week is dedicated to partnering with colleagues in academia, regional cancer registries, clinical practices and private industry to generate research that will ultimately improve the lives of cancer patients.

Katz, who is the director of the Cancer Surveillance and Outcomes Research Team at the Rogel Cancer Center, is inspired to understand how people make decisions when they're diagnosed with cancer and how clinicians navigate those decisions with patients to yield the best possible outcomes.

His research using the National Cancer Institute Surveillance, Epidemiology and End Results

registries in California, Georgia and Michigan looks at how germline genetic testing is being used after diagnosis of cancer across a broad array of patients in the community and the implications for both patients and their families.

"Genetic testing, both somatic and germline, have become important new avenues of the valuable information after diagnosis," Katz says. "We have been leading efforts nationally to understand how testing is being used most appropriately and address the challenges that patients and their clinician are confronting."

In the future, genetic testing should be integrated into the mainstream of clinical decision-making, Katz adds. This includes the broader framework of how clinicians and patients navigate the implications of testing after diagnosis, as well as how patients communicate with potentially at-risk family members about opportunities for genetic risk evaluation.

Katz knows from his research that people have a wide range of reactions to receiving genetic data and whether to share it with at-risk family members. Of equal importance is the communication that takes place between physicians and their patients about test results, and whose responsibility it is to communicate this complex report to others who may be impacted.

"The bottom line is that patients aren't trained to be patients when they're diagnosed with cancer. And now during a difficult time in their lives they have a responsibility to share information about their disease and complex results of genetic testing with family," Katz says. "Clinicians are ultimately responsible for facilitating this communication in order to maximize cancer prevention opportunities for patients and their families."

Analysis of data leads to clinical trials

With genetic testing of cancer patients becoming closer to standard of care for certain cancer types, scientists like Chinnaiyan and others continue to advance their research.

This has led to a new type of clinical trials, known as basket trials, based on patients' individual molecular alterations, rather than cancer type. The Targeted Agent and Profiling Utilization Registry, or

TAPUR, is a national oncology clinical trial aiming to match advanced cancer patients who have received genetic sequencing with one of several possible anti-cancer therapies.

Ajjai Alva, MBBS, associate professor of hematology/oncology at Michigan Medicine, is a principal investigator of TAPUR. The Rogel Cancer Center is a leading accrual location thanks to its collaborative work in genetics across the institution. The study is enrolling patients at 117 clinical sites.

Research is moving toward trying to sequence patients earlier in the course of their cancer, Chinnaiyan notes, before tumors have evolved and developed resistance mechanisms that make them more challenging to treat.

Now, a review of actionable genomic alterations

With Mi-ONCOSEQ providing rich genetic data to mine, Erin Cobain, M.D., clinical lecturer of hematology/oncology at Michigan Medicine, recognized the need for a more robust mechanism for understanding how comprehensive genetic testing impacts clinical outcomes for patients.

"We had all these patients that had been sequenced and presumably their clinicians were using the reports, but we had no idea how it was impacting care," Cobain says. "We looked at 1,300 patients across cancer types who got treatment informed by sequencing to see if anyone had a dramatic impact."

The answer was yes. There were exceptional responders where patients received treatment that wouldn't have been offered otherwise as standard of care for their cancer type; their disease was controlled for longer than expected.

Additionally, as documented in the 2017 *Nature* paper, the study found a high prevalence — around 10–12% — of germline findings, or inherited variants, in patients with advanced cancer.

Cobain found these germline variants in multiple settings:

1. A genetic variant that increased the risk for the cancer a patient has, such as the BRCA1 gene for breast cancer
2. A genetic variant that puts a patient at risk for another cancer
3. A genetic variant that is unrelated to the patient's cancer



Erin Cobain, M.D., and Kenisha Hauser, R.N.

"We're starting to come to the understanding that certain circumstances and criteria to merit genetic testing is a flawed paradigm. We're finding patients that don't meet the classic criteria from a clinical perspective for genetic testing," she says.

These events, though rarer, require further study to understand the true population frequency of events that Cobain describes as finding needles in the haystack.

"One of the ways we might imagine addressing it is asking whether every patient with metastatic cancer merits genetic testing. This is not an answer, but a question that a study like ours will raise," Cobain says. 📌

BETTER COMMUNICATION, BETTER CARE

BY SHELLEY ZALEWSKI

Apps, text messaging, other technology keep cancer patients, families and survivors in the know

Every day, University of Michigan Rogel Cancer Center researchers are developing new ways to treat cancer. Genetic testing to identify those at risk. Next-generation imaging to see it. Precision therapies to target it.

They're also working on new ways to talk about it.

Understanding and treating cancer presents extraordinary communications challenges. Patients can be overwhelmed by information. Providers struggle to bring clarity to complexity. Face-to-face time with clinicians is in short supply. Everyone needs tools to understand their diagnosis and to be understood.

For more than 20 years, developing those tools has been the purpose and passion of the Center for Health Communications Research, also called CHCR, at the Rogel Cancer Center. Cancer clinicians and CHCR experts partner to design and test evidence-based educational and behavior-change interventions. Advances in technology have allowed for the creation of high quality tools using print, mobile device, web-based or other communication channels and strategies.

CHCR is one of more than a dozen shared resources available to researchers at the Rogel Cancer Center. It provides communications expertise and services for research studies requiring targeted and tailored interventions that inform health decisions. The dedicated team of technology experts, behavioral scientists, graphic designers and project managers helps research investigators across a range of services, including:

- Engaging enrollment approaches to optimize trial recruitment
- High quality mobile apps, websites and personalized media
- Behavioral change interventions for investigators conducting research on cancer prevention, control and care delivery

CHCR's latest projects illustrate the power of technology to improve communication and communication to improve outcomes.



Ken Resnicow, Ph.D.



Larry An, M.D.



Sarah Hawley, Ph.D., MPH

Keeping patients informed and connected

For patients looking for answers and advice about cancer treatment, the challenge isn't a lack of information. More often they find themselves overwhelmed by online searches and overloaded with brochures and handouts.

"It's not just too much information; it's often the wrong information," says breast cancer surgeon Michael Sabel, M.D., division chief and William W. Coon Collegiate Professor of Surgical Oncology at Michigan Medicine. "Even when the source is reliable (and many on the web are not), it may not address the patient's specific concern. As clinicians, we wish we could be there 24/7 to answer questions and troubleshoot issues."

While there's no substitute for a one-on-one discussion with a doctor or nurse, Sabel worked with CHCR to develop the next best thing, launching the Breast Cancer Ally mobile app.

Unlike health apps that provide only generic medical content, Breast Cancer Ally asks patients specific questions about their disease stage, treatment plan, symptoms and concerns, and then delivers customized, actionable information. Patients recovering from axillary lymph node dissection are prompted with instructions and reminders to perform arm exercises to improve mobility, while patients undergoing chemotherapy receive tips for managing side effects.

"The app is a clinical companion," says Sabel, "enhancing doctor-patient interaction, not replacing it." Sabel is collaborating with CHCR and other Michigan Medicine partners to develop the next generation Breast Cancer Ally and extend the platform to other cancer types.

"For an even more personalized, just-in-time connection with patients, we're linking to our electronic health information system and adding text messaging functionality," he explains. The goal is to make the app an even more powerful, responsive tool to manage treatment-related side effects before they become serious complications.



Michael Sabel, M.D.



Breast Cancer Ally is a mobile app that serves as a clinical companion to enhance, not replace, doctor-patient interaction.



Patient answers questions online



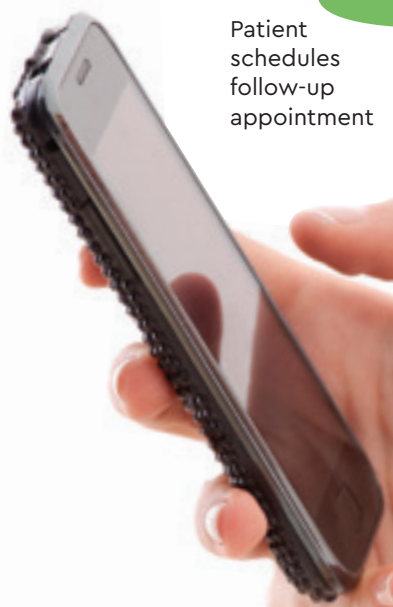
Answers shared with providers



Patient receives tailored educational content



Patient schedules follow-up appointment



Overcoming obstacles to coordinated care

After initial breast cancer treatment, the focus shifts to survivorship care. Patients need both ongoing surveillance and preventive care, as well as support to manage late effects and cope with the psychosocial effects of their cancer.

Team-based cancer care, with well-defined roles and good communication between the oncologist, primary care physician and patient, is the recommended approach to maximize quality and improve outcomes.

But it can be tough to keep patients and providers on the same page.



Lauren Wallner, Ph.D., MPH

With funding from a K07 award from the National Cancer Institute, investigators from the U-M Cancer Surveillance and Outcomes Research Team, known as CanSORT, are collaborating with CHCR to pilot a first-of-its-kind intervention that facilitates team-based breast cancer survivorship care.

The project is led by Lauren Wallner, Ph.D., MPH, assistant professor of general medicine and epidemiology at the University of Michigan, and CanSORT co-directors Steven Katz, M.D., MPH, professor of medicine and health care management and policy, and Sarah Hawley, Ph.D., MPH, professor of general medicine, health care management and policy, health behavior and health education.

The intervention is powered by a patient- and provider-facing, interactive web-based tool called ConnectedCancerCare.

On the website, patients answer questions about treatment and care experiences, provider preferences, concern about recurrence and more. They then receive tailored educational content, including tips on what to expect from and how to communicate with their PCP and oncologist about what happens next with survivorship care. They can learn about regional and national resources for common concerns like financial matters, managing side effects and coping. And they are prompted with email or text reminders to schedule appointments with their primary care physician.

The tool also communicates with the PCP and oncologist, generating letters highlighting the patient's preferences, flagging top concerns and identifying knowledge gaps about provider roles and services.

Surveys conducted three months into a pilot randomized trial reveal high user satisfaction with the tool. Compared with the static survivorship intervention provided to the control group, ConnectedCancerCare was shown to improve provider communication with patients. Patients using it were more likely to schedule guideline-concordant PCP follow-up appointments.

The next step is a large, multi-center trial to evaluate ConnectedCancerCare in general oncology practice settings nationally.

ConnectedCancerCare is for patients and providers to improve communication and understand survivorship care.

Safeguarding the health of our most valuable partners

Patients undergoing hematopoietic cell transplantation — commonly referred to as blood and marrow transplant or BMT — are among the most vulnerable patient populations. These fragile patients are wholly dependent on family caregivers, such as spouses, parents, friends or other non-medical caregivers, throughout their rigorous therapy and journey, starting during the initial hospital stay and continuing well beyond their return home.

In 2014, pediatric hematologist Sung Won Choi, M.D., Edith S. Briskin and Shirley K. Schlafer Foundation Research Professor of Pediatrics at Michigan Medicine, began working with CHCR to develop and test BMT Roadmap, a web-based tool to help caregivers navigate inpatient BMT treatment. Her work was directly informed by her studies of BMT patients enrolled in clinical trials, where she recognized the need to also support the family caregivers upon whom patients were completely dependent during their care.

By leveraging mobile health, or mHealth, technology, her goal was to make care and monitoring easier by providing real-time patient lab results, medication lists, clinical trial details, a photo directory of the health care team, a detailed description of the transplant process, and a discharge checklist, all in one place — at the touch of a screen. This mHealth tool is now being expanded to support caregiving after discharge, where the majority of caregiving takes place without the daily supervision of the health care team.

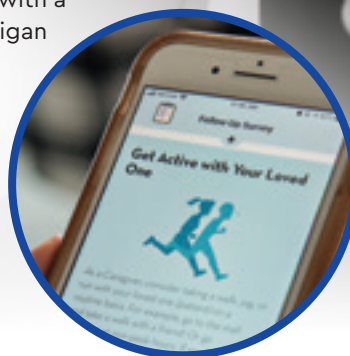
With the next generation of BMT Roadmap, Roadmap 2.0, Choi turned her attention to an unmet need she encountered every day: amid the myriad needs of their recovering loved ones, caregivers often neglected to look after themselves, and in turn, may be overlooked or become ill.

"Caring for a transplant patient takes a physical and emotional toll," says Choi. "Healthier, more resilient caregivers are more likely to make a positive impact over the long journey of transplant and recovery. We need to give them the tools to stay well throughout that journey."

Roadmap 2.0 will be a phone-based mHealth app. To determine the design and features of Roadmap 2.0, Choi's research team interviewed more than 50 patient-caregiver pairs and will combine those insights with data from a national caregiver health survey that captured more than 1,300 BMT caregiver respondents.

An NIH grant funds the project, which will be evaluated with a randomized clinical trial. With collaborators across Michigan Medicine, the team's goal is to leverage mHealth and integrate clinical, physiological and biological data to better understand caregiver health, and how that may ultimately impact patient health.

Sung Won Choi, M.D. led the development of the BMT Roadmap tool to help patients and caregivers navigate inpatient care and recovery.





Ken Resnicow, Ph.D.

Colon cancer screening: turning intention into action

Face it: no one is thrilled about colorectal cancer screening.

Breaking down barriers to screening is the goal of Ken Resnicow, Ph.D., Irwin M. Rosenstock Collegiate Professor of Public Health and associate director for Community Outreach, Engagement and Health Disparities at the Rogel Cancer Center. Resnicow and CHCR collaborators Larry An, M.D., and Sarah Hawley, Ph.D., MPH, have developed a texting intervention to encourage people in need of or overdue for colon cancer screening to take the next step.

The collaborative effort began when the National Cancer Institute created and deployed a text message-based program to promote cancer prevention and control behaviors of healthy diet, exercise and smoking cessation. Through collaboration with U-M in 2017-18, NCI provided the messages to CHCR, who updated the information using local technology. The rebranded U-M program is called Tips4Health and is now offered throughout Michigan with good uptake.

Yet one limitation of the program was that it wasn't individualized to users; everyone got the same messages that were developed by the NCI. And the original suite of programs from NCI — healthy diet, exercise and smoking cessation — did not address a key need of the U-M catchment area, specifically, to improve uptake of colon cancer screening.

Based on existing colorectal cancer screening programs developed by Resnicow, Hawley and the CHCR team, colorectal screening messages were added to Tips4Health, tailored to individual users' knowledge, preferences and barriers to getting screened.

Users are prompted to identify the barriers that make them reluctant to undergo screening. For example, barriers to colonoscopy can include aversion to the preparation, fear of sedation, concerns about missing work or having to bring along a driver.

Tips4Health-CRC Screening now provides content to address each barrier. Additionally, the team reached out to colleagues at Virginia Commonwealth University and Temple University, who had developed tailored video testimonials designed to help patients overcome specific concerns about colon cancer screening. The testimonials were

shared with U-M researchers and added to Tips4Health so users of the app receive text messages with optional video links.

"We're working toward adding 'click to schedule' capability to make a colonoscopy appointment, or the delivery of an at-home test kit (e.g., ColoGuard®) on the spot," says Resnicow. "That's the final step in turning intention into action."

U-M researchers added tailored messages to improve uptake of colon cancer screening.



Bridging the information-comprehension divide

Research shows that patients retain only about a third of what's discussed in a typical doctor visit. So for an overwhelmed patient presented with a cancer diagnosis and asked to evaluate complex treatment options, it's likely even less.

A team led by CHCR co-directors Larry An, M.D., and Sarah Hawley, Ph.D., MPH, has been working with U-M engineering professor Rada Mihalcea, Ph.D., to leverage technologies like artificial intelligence (AI) and natural language processing (NLP) in next-generation doctor-patient interventions. These technologies use algorithms to understand human speech.

"AI and NLP help people interact with technology the same way we interact with each other — by speaking and listening, not pointing and clicking," An says.

An's moment of realization about AI's potential came at a symposium hosted by Mihalcea where they met Scott Huffman, vice president of engineering at Google, who is responsible for the company's AI-based virtual helper, Google Assistant.

"People are welcoming agents like Google Assistant, Amazon's Alexa and Apple's Siri onto their phones and into their homes because they make life easier," An says. "Could they make it easier for cancer patients to comprehend, retain and act on information from clinic visits?"

Encouraged by Huffman, they applied for and earned a Google Focused Award to find out. The awards are for research in areas of key interest to Google, as well as the research community. They are unrestricted gifts that typically last for two to three years. Recipients have the advantage of access to Google tools, technologies and expertise.

Still in its infancy, their trial (targeted for early 2020) will put a cancer-trained version of Google Assistant on a patient's smartphone or other device. In the consult room, it will listen, record and transcribe. At home, the patient can search the transcript to revisit specific issues ("What did the doctor say about my lymph nodes?"), navigate cancer terminology ("What are lymph nodes, anyway?") and more.

Clinicians across the Rogel Cancer Center have shared even more possible applications for the Assistant. The technology could help prepare patients for clinic visits, learning their top concerns in advance and ensuring they are addressed. It could also improve inpatient unit communications, when coordinating dialog between patients, rounding specialists and visiting family members is challenging.

"When patients don't retain information, much of the value of health care leaks away," says An. "AI has the potential to restore that value on demand."



Larry An, M.D., and Sarah Hawley, Ph.D., MPH

SEE CHANGE

Technologies developed by the Rogel Cancer Center offer promise for early detection, and better monitoring and management of cancer

BY IAN DEMSKY

ON A SCREEN IN HIS OFFICE, THOMAS WANG, M.D., PH.D., WATCHES AS AN ENDOSCOPE SLIDES DOWN THE PALE, SMOOTH TUNNEL OF AN ESOPHAGUS. THE TISSUE IS UNREMARKABLE, PINK AND HEALTHY LOOKING. "NOW WATCH THIS," SAYS WANG, A PHYSICIAN-SCIENTIST AT THE UNIVERSITY OF MICHIGAN, NUDGING THE VIDEO FORWARD. A BLUE LIQUID SQUIRTS INTO THE FRAME, COATING THE PASSAGE. THE LIGHTING SHIFTS FROM FLAT, WHITE LIGHT TO NEAR-INFRARED LIGHT. A PATCH OF CELLS ON ONE SIDE OF THE ESOPHAGUS FLUORESCES PINK AND PURPLE — AN INDICATION OF PRE-CANCEROUS CHANGES INVISIBLE TO THE NAKED EYE.

"Molecular imaging is an emerging technique that has potential to improve the early detection of a variety of cancers — esophageal, colorectal, stomach, biliary tract, pancreatic, bladder — that develop in the epithelial tissue of hollow organs," says Wang, professor of internal medicine, bioengineering and mechanical engineering at U-M.

The liquid contains a peptide developed by Wang's research team. It selectively binds to receptors on the surface of cells that have undergone transformations in response to chronic stress and genetic changes. In this case, the peptide zeros in on epidermal growth factor receptor (EGFR) proteins, which are overexpressed in high-grade dysplasia, a precursor of esophageal cancer.

Cancer prevention guidelines recommend that patients with high-risk conditions receive traditional endoscopy at regular intervals to look for diseased tissues, along with having random samples from their esophagus biopsied to check for microscopic changes. The instantaneous optical biopsies that Wang's group is developing would take much of the guesswork out of this process.

"If we can see these damaged cells before they become cancerous, we can resect or ablate them," Wang says. "It's much better to prevent cancer than to treat and manage it after it develops."

U-M is one of three translational research centers across the country that are part of the National Cancer Institute's Barrett's Esophagus Translational Research Network (BETRNet) — a multi-disciplinary, multi-institutional collaboration to centralize and enhance efforts to understand Barrett's esophagus, another precursor to esophageal cancer.

Along with reporting the first-in-human trials results of the technique for detecting esophageal cancer, Wang's team has also applied this approach in colorectal cancer, and is in the initial stages of further developing some of the lab's peptides for broader clinical trials.

They're also in the process of commercializing a miniaturized microscope they developed — about 2 millimeters wide — that can be threaded through an endoscope to analyze tissue samples in real time. Not only does this save the time of sending them out to a pathologist for review, it could often save patients a return visit if something concerning is discovered, he says.

"Engineering an instrument like this is possible because of the amazing resources and cross-disciplinary collaborations that are only available in a place like U-M," Wang adds.



A wearable biopsy alternative

Wearable devices are increasingly used to monitor many aspects of our health — sleep patterns, heart health, menstrual cycles, even alerting us to rising decibels that could damage our hearing. A team of doctors and engineers from U-M believe they could also help to monitor cancer.

The U-M researchers developed a prototype for a wearable device that can continuously collect live cancer cells from a patient's blood, providing a next-generation alternative to traditional biopsies used to collect and evaluate tumor cells circulating in the blood.

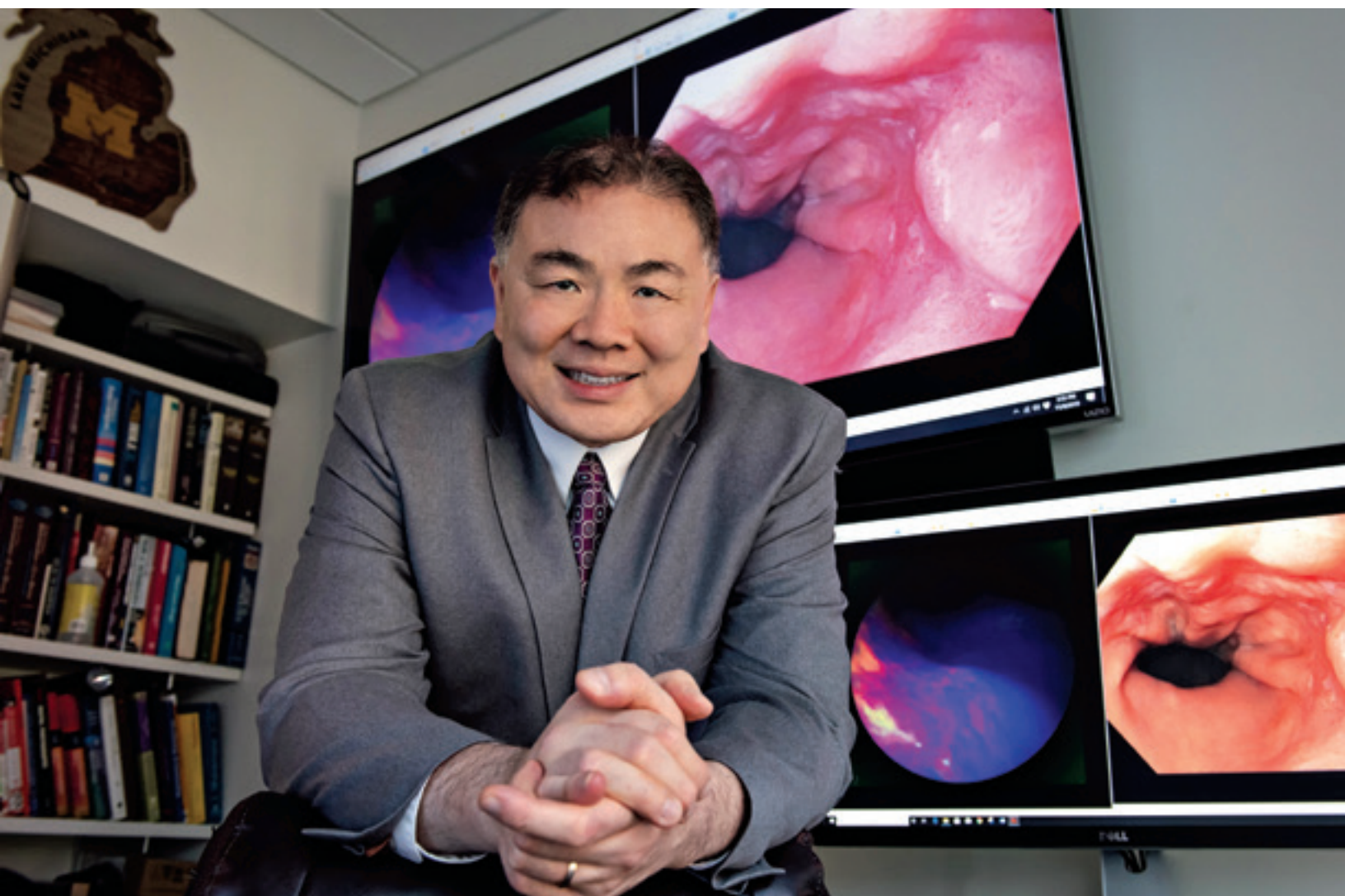
Studying cancer cells captured from blood is known as a liquid biopsy. These are more convenient than a traditional tissue biopsy, requiring only a blood draw, and could provide better information for planning treatments.

Tumors can release more than 1,000 cancer cells into the bloodstream each minute, says Daniel F. Hayes, M.D., Stuart B. Padnos Professor of Breast Cancer Research, who worked on the project. Many regular blood draws, however, come back with no cancer cells, even in patients with advanced cancer, and a typical sample contains no more than 10 cancer cells.

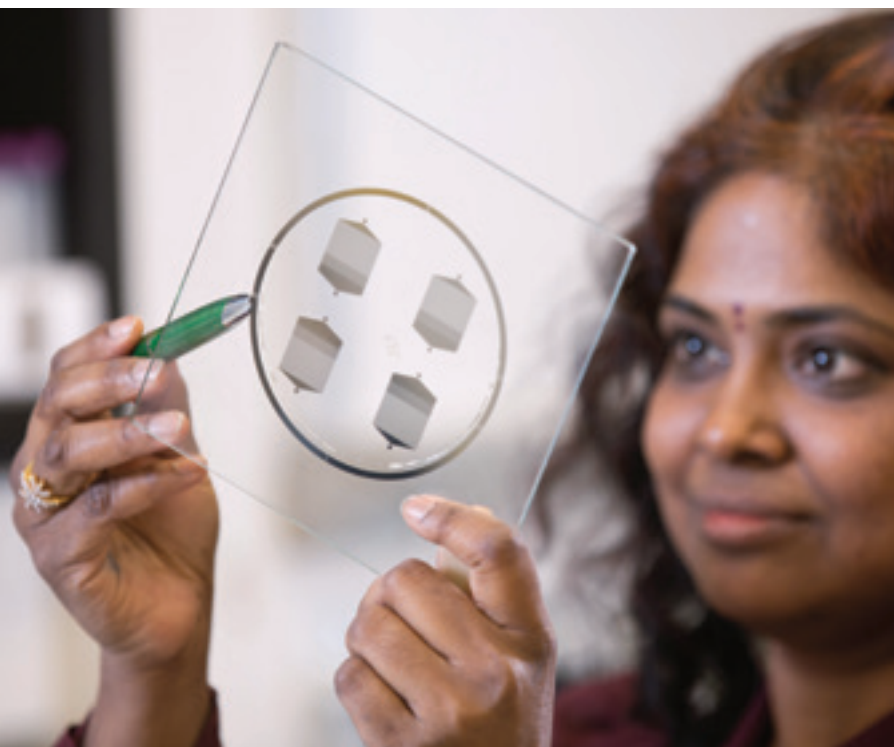
The new device, about the size of an iPhone, is designed to capture cancer cells continuously over several hours through a catheter inserted into a patient's vein. In animal models, the cell-grabbing chip in the wearable device trapped three and a half times as many cancer cells per milliliter of blood than the standard approach, according to results published in *Nature Communications*.



Daniel F. Hayes, M.D.



Thomas Wang, M.D., Ph.D.



Sunitha Nagrath, Ph.D.

"It's the difference between a security camera that takes a snapshot of a door every five minutes or one that takes a video. If an intruder enters between the snapshots, you wouldn't know about it," says Sunitha Nagrath, Ph.D., associate professor of chemical engineering at U-M, whose lab developed the device.

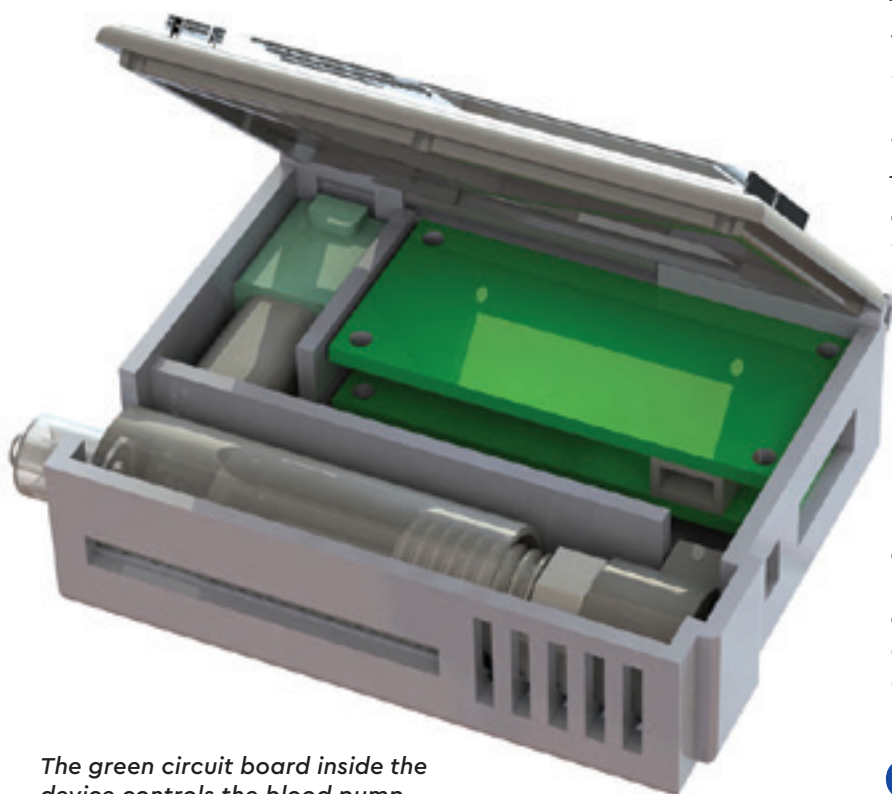
The device is small enough to be worn on the wrist, as opposed to a machine that is typically the size of an oven. A wearable device allows the patient to be mobile during collection. For help with the smaller design, the engineering team turned to Laura Cooling, M.D., professor of clinical pathology at U-M, and associate director of the blood bank, where she manages the full-size systems.

"The most challenging parts were integrating all of the components into a single device and ensuring the blood would not clot, that the cells would not clog up the chip, and that the entire device is completely sterile," says Tae Hyun Kim, Ph.D., who earned his doctorate in electrical engineering while working in the Nagrath Lab and is now a postdoctoral scholar at the California Institute of Technology.

The team developed protocols for mixing the blood with heparin, a drug that prevents clotting, and sterilization methods that killed bacteria without harming the cell-targeting immune markers, or antibodies, on the chip.

The chip itself is a new twist on one of the highest-capture-rate devices from Nagrath's lab. It uses the nanomaterial graphene oxide to create dense clusters of antibody-tipped molecular chains, enabling it to trap more than 80% of the cancer cells from the whole blood that flows across it. The chip can also be used to grow the captured cancer cells, producing larger samples for further analysis.

In the next steps for the device, the team hopes to increase the blood processing rate and estimates the device could begin human trials in three to five years. It would be used to help optimize treatments for human cancers by enabling doctors to see if a patient's cancer cells might be good candidates for specific, targeted therapeutics.



The green circuit board inside the device controls the blood pump, heparin injector and display data.

Illustration by Tae Hyun Kim

It traps more than 80% of the cancer cells from the whole blood that flows across it.

Setting a trap for cancer cells

In most cancers, the emergence of metastases marks the shift from trying to cure a patient's disease toward efforts to extend their life.

Jacqueline Jeruss, M.D., Ph.D., a breast cancer surgeon, and Lonnie Shea, Ph.D., a biomedical engineer, have developed a tiny, implantable, porous disc that aims to catch aggressive cells as they first begin to migrate — long before a cough, pain or other systems reveal a patient's cancer has overtaken vital organs.

In addition to the potential for early detection of distant recurrence, animal model studies show the implant, which the researchers call a scaffold, may even be able to slow the progress of metastasis by attracting and trapping aggressive cells, thus preventing them from reaching distant organs.

"In my practice, I see patients with aggressive cancer subtypes who are treated with surgery, chemotherapy and radiation, and many of them can be initially rendered disease-free. Unfortunately, some of these patients will eventually develop distant metastasis," says Jeruss, associate professor of surgery and biomedical engineering. "We know many cancer patients have tumor cells harbored in their bodies, and the immune system may eliminate these cells or the cells remain dormant

for many years. We aimed to identify the cancer cells that, over time, graduate to that next stage of aggressiveness and become a metastasis, so we can target them directly."

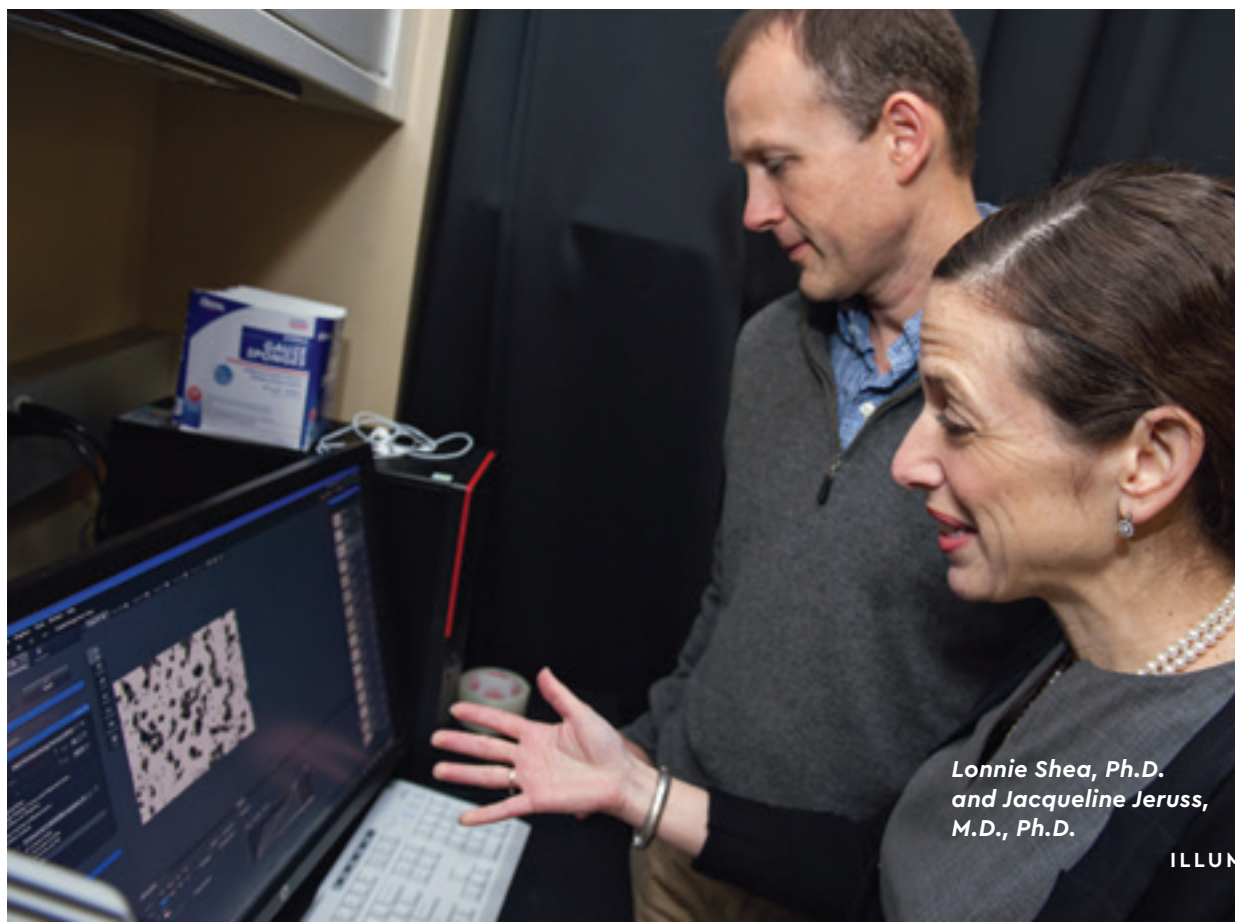
The implant is 5 millimeters across — about the same diameter as a pencil eraser — and 2 millimeters thick. It is made from a biodegradable polymer called poly(ϵ -caprolactone), a Food and Drug Administration-approved material used for sutures and wound dressings.

5mm x 2mm

The scaffold is designed to be implanted in the subcutaneous tissue of the abdomen in an outpatient setting using a local anesthetic.

Once installed, the body mounts an immune response to the foreign substance. In healthy mice, the response to the surgery and the device causes some minor inflammation.

"But in mice with cancer, the immune cells in the blood have changed. These immune cells in the blood are drawn to the implant, and as a consequence, this environment then draws in the tumor cells from the vasculature that has grown into the device," says Shea, William and Valerie Hall Chair of Biomedical Engineering.



*Lonnie Shea, Ph.D.
and Jacqueline Jeruss,
M.D., Ph.D.*

"THIS DEVICE COULD HELP
PROVIDE A WINDOW INTO AN
INDIVIDUAL PATIENT'S IMMUNE
FUNCTION AT A METASTATIC SITE."

—Lonnie Shea, Ph.D.



The cells captured by the scaffold had significantly more aggressive metastatic properties compared to cells obtained from the primary tumor, and closely resembled cells from lung metastases, the team announced in *Cancer Research*.

The nature of the implant makes it easy to monitor.

"Using the scaffold, we can ideally monitor the patient's disease course through ultrasound, core biopsy or by removing the implant — rather than performing more invasive biopsies of lung, liver or bone," Jeruss says.


Because they were focused on early detection of distant recurrence and the potential for an analysis of captured cells to recommend or develop targeted therapies, the researchers were intrigued to also find that the implant reduced the cancer burden in solid organs of animal models as well.

Fifteen days after tumor initiation, mice with the implants had 64% fewer cancer cells identified in the liver and 75% fewer cancer cells in the brain, when compared to mice that did not receive the scaffolds, the team reported in 2016.

"It makes sense," Shea says. "The scaffold is capturing many of those cells and taking them out of circulation."

A proposal for an initial clinical study of the implant in metastatic cancer patients is under review by the FDA.

Shea stresses the device's additional potential to help tailor immunotherapy to individual patients: "Immunotherapy is taking cancer treatment by storm. There's a tremendous opportunity to help patients, but this treatment approach is not always successful and it's not clear why. This device could help provide a window onto an individual patient's immune function at a metastatic site, to look at what is suppressing the immune system and potentially tailor the nature of the therapy to block that suppression."

In a blog post, National Institutes of Health Director Francis S. Collins, M.D., Ph.D., called the work a "creative marriage of engineering and medicine," writing: "[T] his new device... is another promising step in the quest to fight metastatic cancer." 

U-M College of Engineering writer Kate McAlpine contributed to this article.

RESEARCH RECAP

"There is a particular need for modeling in the current environment, in which people are using many different forms of tobacco — cigarettes, cigars, chewing tobacco, etc. — and increased availability and use of alternative nicotine delivery products, such as e-cigarettes." -Rafael Meza, Ph.D., on the \$20 million grant from the National Institutes of Health and Food and Drug Administration's Tobacco Centers of Regulatory Science to generate critical research that informs the regulation of tobacco products.

\$20M
grant



In a study of inflammation and colon cancer in mice, researchers found neutrophils — immune cells in the colon cancer tumor microenvironment — slowed colon cancer growth. Using a genetic strategy to inactivate neutrophils, they identified genes that regulated antimicrobial and inflammatory processes when neutrophils were not depleted in control mice. Neutrophils slowed cancer tumor progression by restricting both numbers of bacteria and inflammatory responses of the tumor.

Gastroenterology, April 2019, Nunez, Colacino, Shah

Long Interspersed Element-1, also called L1, sequences make up around 17% of the human genome. A study of more than 88,000 engineered L1 insertions in five human cell lines found that L1 insertions do not target genes, transcribed regions or open chromatin. Compared to a null model, acquisition of an endonuclease domain, in conjunction with the ability to integrate into replicating DNA, allowed L1 to become an autonomous, interspersed retrotransposon.

Cell, May 2019, Ljungman, Moran

Pancreatic cancer researchers asked: Why does gemcitabine, a frontline chemotherapy drug, work pretty well in some cancers but not in pancreatic cancer?

Research found: Tumor-associated macrophages release compounds that block gemcitabine in the most common type of pancreatic cancer.

Cell Metabolism, March 2019, Frankel, Crawford, Pasca Di Magliano, Lyssiotis

Researchers cataloged circular RNA in multiple cancers and found these stable structures could serve as cancer biomarkers in blood or urine. The team identified several circRNAs in prostate cancer tissue, which could be potentially useful for cancer diagnosis or prognosis.

Cell, February 2019, Cieslik, Nesvizhskii, Chinnaiyan

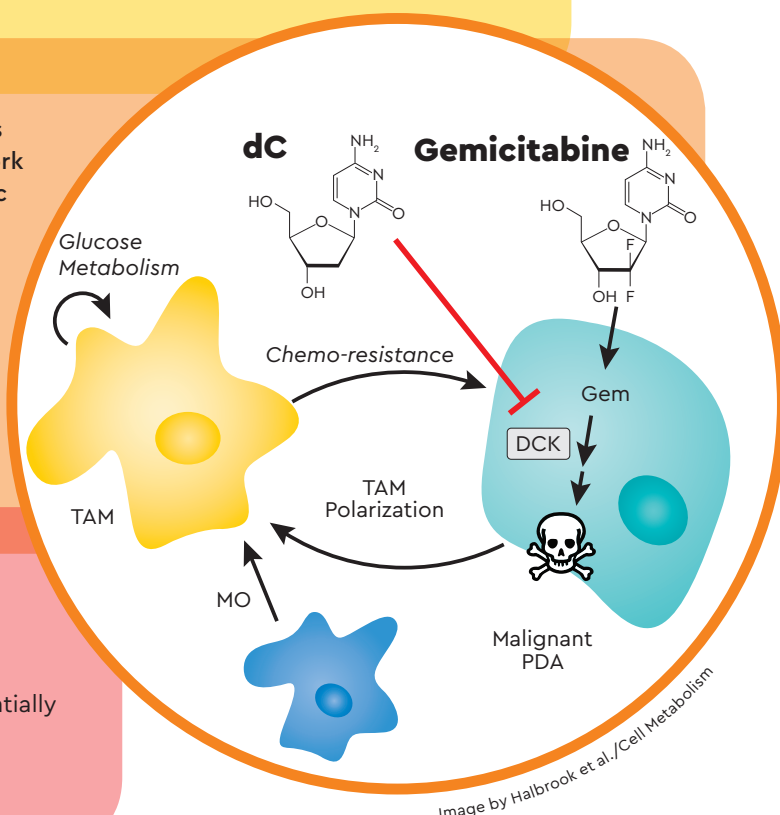


Image by Halbrook et al./Cell Metabolism

"If we can intervene early in this diagnosis, before the tumor comes back more aggressive and deadly, it could have a big impact for these patients." Maria G. Castro, Ph.D., on new research that found a genetic mutation — IDH1 — seen in about half of all brain tumors produces a response that prevents radiation treatment from working.

Science Translational Medicine, February 2019, Koschmann, Calinescu, Ljungman, Qin, Sartor, Venneti, Zhao, Lyssiotis, Lowenstein, Castro



A U-M study is the first to define how ferroptosis — a type of cell death dependent on iron — is linked to cancer cell death and immune cells, concluding that the combination of a ferroptosis sensitizer and checkpoint inhibitor creates a strong immune response that fights the tumor by causing ferroptosis.

Nature, May 2019, Green, Liu, Lawrence, Cieslik, Chinnaiyan, Zou



"In mice when we knocked out NLRP6, instead of doing worse, they did better. That was a big surprise." -Pavan Reddy, M.D., on a study that found the protein NLRP6, which usually has a protective role, aggravated symptoms of graft-versus-host disease after bone marrow transplant.

Nature Microbiology, March 2019, Riwes, Chen, Reddy

In a study to investigate the therapeutic potential of protein disulfide isomerase (PDI) to overcome resistance to chemoradiation in patients with glioblastoma multiforme, researchers found that a novel mechanism involving downregulation of DNA repair genes demonstrated efficacy of PDIA1 inhibition in combination with radiotherapy.

Cancer Research, June 2019, Ljungman, Neamati, Rehemtulla

\$9.2M
SPORE grant

The Rogel Cancer Center, along with the Barbara Ann Karmanos Cancer Institute at Wayne State University, received a prestigious \$9.2 million SPORE grant from the National Cancer Institute to focus on critical questions of how prostate cancer develops, with projects designed to address major barriers and challenges in diagnosis, treatment and metastasis.

"If we're ever going to cure pancreatic cancer, we're going to need effective systemic treatment as well as local therapy. Our data suggests that AZD1775 can do both." -Ted Lawrence, M.D., Ph.D., on an early clinical trial finding that a Wee1 inhibitor, combined with radiation and gemcitabine, is safe and potentially effective in pancreatic cancer treatment.

Journal of Clinical Oncology, August 2019, Cuneo, Morgan, Sahai, Schipper, Al-Hawary, Cho, Nathan, Maybaum, Zalupski, Lawrence



SEE

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R

ARCH

Prostate cancer researchers aimed to identify factors associated with the adoption of sipuleucel-T, an immunotherapy, across the United States. They found disparities in dissemination of the novel therapy tied to race, geography, income and type of physician.

JAMA Network Open, April 2019, Caram, Mukherjee

Rogel Cancer Center researchers found that the gene FOXA1 overrides normal biology in three different ways to drive 35% of prostate cancers. They refer to the three classes as FAST, FURIOUS and LOUD to reflect their unique features. The three alteration classes have different clinical implications for patients.

Nature, June 2019, Cieslik, Chinnaiyan



In the case of long-term surveillance of treated, low-risk thyroid cancer, patients categorized as maximizers consume more health care resources — such as doctor visits and diagnostic imaging tests — which drive up costs without a clear improvement in outcomes.

Journal of Clinical Oncology, October 2019, Banerjee, Wallner, Hawley, Zikmund-Fisher, Haymart

The Forbes Scholars program increases the pace with which innovative laboratory discoveries are transformed into new patient treatments and establishes a university-wide cohort of researchers committed to cancer discovery. In 2019, funding for high-risk, high-reward cancer research went to:

- Clifford S. Cho, M.D., and Zhen Xu, Ph.D., histotripsy tumor ablation: a trigger to expand the efficacy of cancer immunotherapy
- David Markovitz, M.D., and Alnawaz Rehemtulla, Ph.D., a molecularly modified lectin for pharmacologic and immune therapy of non-small cell lung cancer
- Daniel Wahl, M.D., Ph.D., Sriram Chandrasekaran, Ph.D., Jason Heth, M.D., Costas Lyssiotis, Ph.D., and Sriram Veneti, M.D., Ph.D., mapping metabolic rewiring in brain tumors in vivo



25
articles

Chad Brenner, M.D., compiled "Applications of Bioinformatics in Cancer," 25 articles by international leaders of bioinformatics and biostatistics that collectively demonstrate that machine learning approaches can be used to make significant advances in cancer biology.

The largest study of its kind finds societal factors and access to quality care — rather than genetics — underlies higher prostate cancer mortality rates for black men, who are more likely to be diagnosed with prostate cancer and nearly 2.5 times more likely to die of the disease compared to non-Hispanic white men.

JAMA Oncology, October 2019, Morgan, Mehra, Salami, Schipper, Spratt

Researchers asked: Is there a connection between life purpose and all-cause or cause-specific mortality among people older than 50?

Research found: a national cohort of 6,985 adults showed life purpose was significantly associated with all-cause mortality. Stronger life purpose was linked to decreased mortality, suggesting purposeful living may have health benefits.

Journal of Medical Oncology, May 2019, Fleischer, Mondul, McLean, Mukherjee, Pearce

6,985
adults

Breast and ovarian cancer researchers found fewer than 25% of breast cancer patients and a third of ovarian cancer patients in two states underwent genetic testing for cancer-associated mutations, indicating a substantial gap between national guidelines for testing and actual testing practice.

Journal of Clinical Oncology, April 2019, Katz

The Rogel Scholars program provides a new support mechanism for exceptional faculty dedicated to achieving impact on cancer prevention, patient outcomes and quality of life.

- Joshi Alumkal, M.D.: Understanding how genomic and epigenomic changes contribute to treatment resistance
- Maria Castro, Ph.D.: Understanding the tumor microenvironment and immune system in brain tumors
- Jolanta Grembecka, Ph.D.: Development of small molecule inhibitors of proteins involved in cancer
- Steven Katz, M.D., MPH: Understanding the impact of genetic risk evaluation and management on cancer treatment decisions
- Judith Leopold, Ph.D.: Designing and developing small molecules to inhibit cancer
- Mats Ljungman, Ph.D.: Exploring the role of the RNA exosome as a target for cancer therapy
- John Magenau, M.D.: Developing clinical strategies to improve the safety and efficacy of blood and marrow transplants for treatment of blood cancers
- Sami Malek, M.D.: Uncovering biomarkers and new pathways to create novel treatments for leukemias and lymphomas
- Sofia Merajver, M.D., Ph.D.: Identifying and targeting factors that make cancers highly aggressive
- Rafael Meza, Ph.D.: Characterizing the impact of cancer prevention and control interventions to inform policy and improve health
- Bhramar Mukherjee, Ph.D.: Developing new methods to analyze large scale epidemiologic data
- Sunitha Nagrath, Ph.D.: Developing technologies to establish liquid biopsy for early diagnosis of cancer and early detection of recurrence
- Marina Pasca Di Magliano, Ph.D.: Understanding the role of the tumor microenvironment in pancreatic cancer
- Tycel Phillips, M.D.: Testing new therapeutic approaches in clinical trials for patients with lymphoma
- Yatrik Shah, Ph.D.: Understanding how low oxygen levels activate genes involved in metabolism, cell survival and iron metabolism in cancer



CANCER SCIENTISTS OF THE FUTURE

Elizabeth Lawlor, M.D., Ph.D., with students April Apfelbaum and Jennifer Jimenez, says mentorship is a crucial aspect of training and education at U-M.

BY BETH UZNIS JOHNSON

Strong mentorship and sponsorship leads to promising careers



Elizabeth Lawlor, M.D., Ph.D.

Elizabeth Lawlor, M.D., Ph.D, believes that stronger lines of communication between cancer disciplines are one important way to expedite the translation of research discoveries into the clinic.

After all, discoveries that are impactful in the lab are not impactful to society until a drug, for example, is developed and approved by the Food and Drug Administration and made available to patients.

This process takes years and ultimately requires a change in clinical practice if broad impact is to be realized.

"People who do cancer research include those who work with the very smallest molecules and cells, to those studying entire populations of individuals. These researchers speak very different languages and have very different backgrounds," says Lawlor, associate director for education and training at the Rogel Cancer Center. "The best time for cancer researchers to learn how to communicate with one another is during their training."

500+
researchers

One especially important aspect, she adds, is mentorship of the next generation of cancer scientists. With more than 500 researchers at the Rogel Cancer Center, nearly everyone does some sort of mentoring of emerging physicians or scientists.

"As mentors, it is critical that we impart not only knowledge in our own specific area of research, but also how to collaborate across disciplines to move science forward. Mentoring is inherent in what we do every day," Lawlor says.

Reshma Jagsi, M.D., D.Phil., can attest to the strong mentorship program in radiation oncology at Michigan Medicine. Mentored as a junior researcher by Lori Pierce, M.D., Jagsi received tenure in 2013 and now conducts breast cancer research across the spectrum of care in addition to research in health services, cancer care delivery outcomes, bioethics and gender equity in the medical profession.



Reshma Jagsi, M.D., D.Phil.

Jagsi now mentors Christina Chapman, M.D., who she describes as "the type of talent our field is going to benefit from in the future." Chapman wanted to research whether black women might benefit from different breast screening guidelines, and Jagsi connected her with an external contact, which led to Chapman receiving NIH funding to execute the project.

And, she linked Chapman with the Michigan Radiation Oncology Quality Consortium to further her work in racial disparities in breast cancer treatment. Pierce is also involved in MROQC, bringing together three generations of radiation oncology mentorship.

"I studied career development in medicine and it opened my eyes to the importance of mentorship and helping someone articulate their goals and what skills they need to build," Jagsi says.

From undergraduate and graduate students to post-doctoral researchers and beyond, the Rogel Cancer Center aims to provide venues and opportunities for research trainees to speak to each other, learn through mentorship, identify gaps in knowledge and work together to fill those gaps.

6
training grants

The cancer center has six training grants funded by the National Cancer Institute that target very specific groups of trainees.

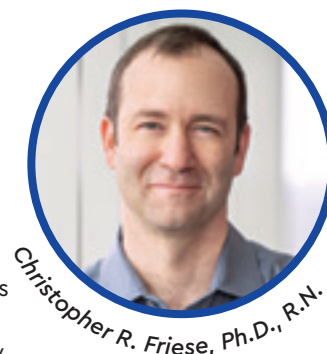
"Research education and training is integral to all aspects of our mission, and we fund it through a diverse array of sources that range from federal grants to philanthropy. The transdisciplinary aspect of our training experience here at U-M is key and what sets us apart," Lawlor says.

Here are some examples of the productive scientific partnerships between mentors and mentees working to advance cancer science at the Rogel Cancer Center.



Quality nursing care begins with informed science

The National Academy of Medicine has cited a shortage of both oncology nurses and nursing faculty. Christopher R. Friese, Ph.D., R.N., associate director for cancer control and population sciences at the Rogel Cancer Center, believes a solution to bridge the gap starts with bringing oncology nurses into the workforce with expertise in both clinical work and research.



Christopher R. Friese, Ph.D., R.N.

"You can't have high quality nursing care without high quality nursing science to inform that practice. It's clinically informed science and scientifically informed clinical practice," says Friese, Elizabeth Tone Hosmer Professor of Nursing and professor of health management and policy at the University of Michigan.

The University of Michigan School of Nursing offers a three-year Ph.D. program involving rigorous coursework in research methodology and theory. Doctoral students are paired with a faculty mentor and embedded into a funded research team throughout the program.

"Being able to mentor the clinical nursing staff and think about their advancing careers, or help them answer tough questions on the floor and apply the evidence base we have, and seeing the problems that patients and nurses and doctors face is very valuable," Friese says. "We are then able to bring that back to my research team to systematically study it and improve it. It's a really nice synergy."

Alex J. Fauer, R.N., is a third-year student who moved into the Ph.D. program directly from U-M's bachelor of science in nursing program. He was a part of Friese's team from day one to begin mastering the practice of research and learning the methods and theory he'd need in order to launch his own research in the future.

"I was confident that Chris would be a strong mentor to help me develop my skillset in quantitative cancer care delivery research and health policy," Fauer says. The two had worked together during Fauer's undergraduate studies on a grant to study hazardous drug exposures for nurses. Fauer presented findings on chemotherapy spills to the Oncology Nursing Society.

In the Ph.D. program, Fauer is part of Friese's research team to assess the impact of communications and technology use on health care quality in outpatient chemotherapy centers across Michigan. Fauer led visits to eight clinical practices to observe clinical care; he interviewed doctors, nurses and patients about their experiences to get a better understanding of opportunities to improve communication.

"About 7% of patients in the study had to go to the ER or have unscheduled clinic visits to manage their side effects," Friese says. "There's an important opportunity there to prevent toxicities from getting so bad that they need extra aggressive treatment."

Friese says a goal of his mentorship is to demonstrate to Fauer that you can remain clinically grounded as you launch a research program.

In 2019, Fauer received a prestigious American Cancer Society Doctoral Degree Scholarship

and is immersed in the data analysis phase of his dissertation to understand the patient experience with care and health care utilization among older adults diagnosed with leukemia and lymphoma.

Fauer will join the National Clinician Scholars Program at UCLA as a postdoctoral fellow after completion of his Ph.D.

Meanwhile, Friese's team continues work on technology and communication in medical oncology practices across Michigan, among other projects. His team also received an education training grant from the National Cancer Institute that funds full-day workshops on chemotherapy safety training for nurses and pharmacy teams.

Collaboration to uncover the complexities of pancreatic cancer

Pancreatic cancer is one of the deadliest human malignancies, with a five-year survival rate still in the single digits. But pancreatic cancer researchers do have scientific reason for hope, as the five-year survival rate, though low, has recently doubled.

This is where mentorship and team science come in.

Timothy Frankel, M.D., assistant professor of surgery at Michigan Medicine, studies tumor immunology as it pertains to pancreatic cancer. His focus is on both immune resistance to cancer and parts of the immune system that may cause it.

Filip Bednar, M.D., assistant professor of surgery at Michigan Medicine, was drawn to the epigenetic regulation of the pancreatic tumor microenvironment because there is much to learn about the biology of this complex disease.

Both scientists are mentored by Marina Pasca Di Magliano, Ph.D., associate professor of surgery and cell and developmental biology at Michigan Medicine. She believes science is shifting to a team enterprise so that, while individual researchers are moving toward the next steps in their careers, teams can engage in complementary work to move science forward faster.

"I mentor junior faculty, graduate students, undergrads and postdocs. If people have mentorship they will do well. It is much more efficient if you don't make the mistakes others

Christopher Friese, Ph.D., R.N., mentors Ph.D. nursing student Alex Fauer, R.N., and sees the value of clinically informed research and vice versa.



before you have made," Pasca Di Magliano says.

And, she adds, she learns just as much from the scientists she mentors as they learn from her.

"The work that's being done feeds in to a lot of different clinically relevant aspects of pancreatic cancer," Bednar says. "We're going to potentially, as a group, contribute new information in screening and early diagnosis. In terms of treatment, all of us are working on different aspects of understanding how the immune system works or doesn't work in pancreatic cancer."

In her research to pursue mechanistic studies to dissect the cellular cross-talk in the pancreatic cancer microenvironment, Pasca Di Magliano saw an opportunity to move from mouse models to human samples.

She has been instrumental in collaborative efforts to build a pipeline to perform single-cell sequencing and mass cytometry on pancreatic tumor samples and matched blood, as well as pancreatitis and healthy blood.

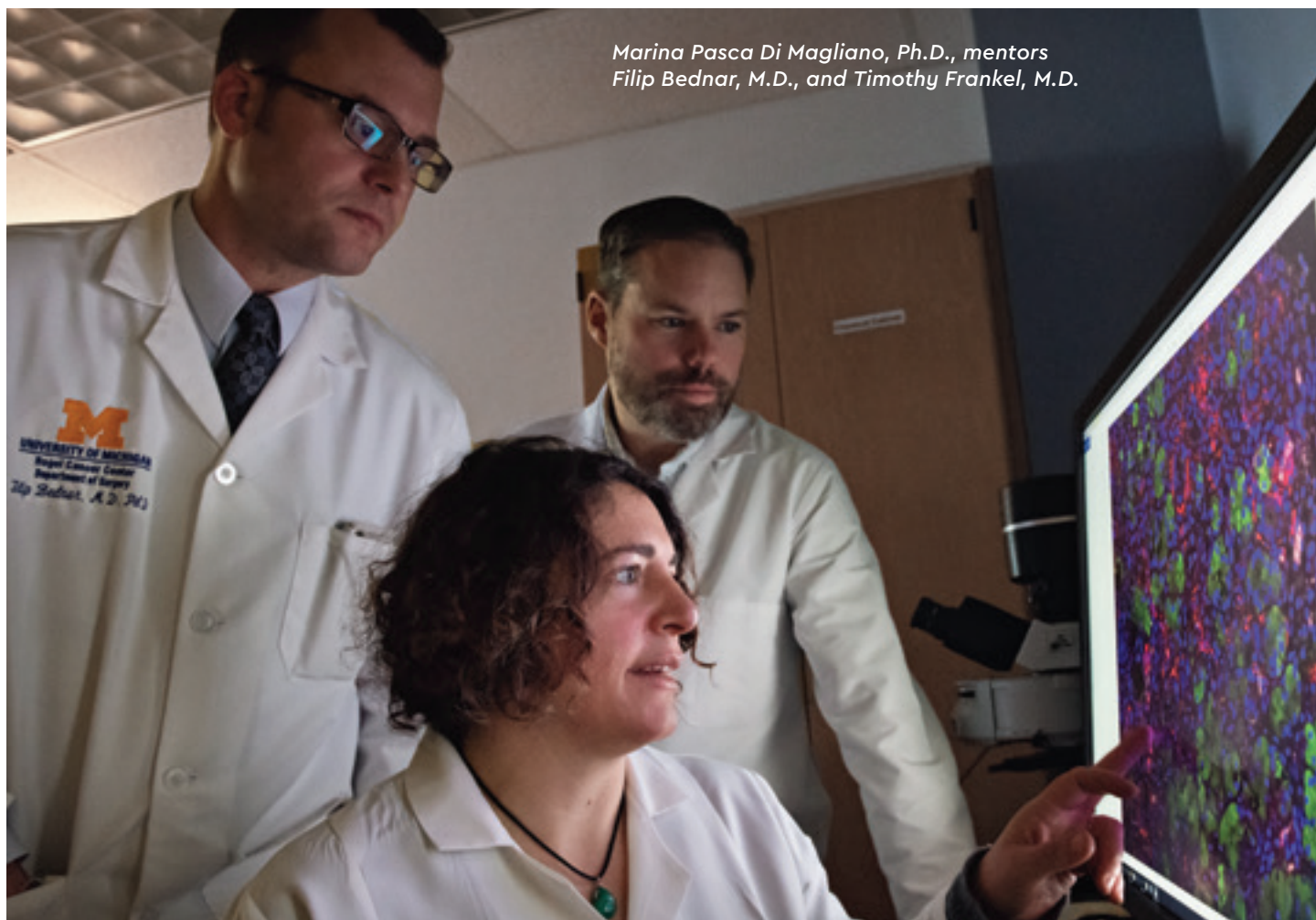
"We are sequencing all the different tumor cells in the microenvironment," she explains.

"We are mapping how they're interacting with one another and can see what genes tumor cells have and what genes immune cells have."

Initial analysis has revealed a profound difference in the immune composition of peripheral white blood cells in pancreatic cancer patients versus healthy individuals. The pancreatic research team hopes to follow patients over the long term post-treatment, as well as identify at-risk patients.



Marina Pasca Di Magliano, Ph.D.



*Marina Pasca Di Magliano, Ph.D., mentors
Filip Bednar, M.D., and Timothy Frankel, M.D.*

Bednar and Frankel agree that Michigan Medicine and the Rogel Cancer Center are a great place to build a career focused on academics blended with clinical care. In addition to labs in close proximity that allow for close collaboration, the Department of Surgery requires contracts for surgeon scientists that name both a clinical mentor and basic science mentor.

"More and more through the years, our labs almost run seamlessly, but there are fringe elements that are independent," Frankel says. "The further along I move in my career, it's starting to shift from mentor to colleague. As that happens, Marina will mentor me to become a mentor."

Striving for social justice and health equity

Anyone with an interest in disparities research understands the constant struggle with sample sizes. Most studies in the 1970s and '80s in the United States did not have racial or ethnic diversity. For young disparities researchers starting careers, finding mentorship can also be challenging, as many in this field are often from minority backgrounds who are — by definition — underrepresented.



That didn't stop Jagsi, Newman Family Professor and deputy chair of radiation oncology at Michigan Medicine, from pursuing research on disparities, bioethics and gender equity.

One of her first large research grants was to study career development in medicine.

"That opened my eyes to the importance of

mentorship. I began studying it and wrote papers on the power of mentor networks and sponsorship," Jagsi says.

Mentorship, she says, is helping someone articulate their goals and build the skills they need to address their research problems. Sponsorship is more about putting your own reputation on the line to give a protégé a chance to shine.

It was one of Jagsi's own mentors, a former professor from Harvard who was serving as a visiting professor, who encouraged her to work with Christina Chapman, M.D., who was then a resident and is now a faculty physician-researcher at Michigan Medicine and the VA Ann Arbor Healthcare System. They met to discuss, among other things, Chapman's interest in using simulation modeling to investigate whether African American women should have breast cancer screening guidelines different than the overall population.

"Christina was ready to dive into a data set and discovered there were no data sets of screening trials that contain sufficient numbers of African American women to actually investigate the important topic she had identified as a research question," Jagsi says.

Jagsi introduced her to an investigator at Georgetown University for the information she needed. Chapman brought forward suggestions and later wrote about ways to better promote equity in physician graduate medical education. They have been mentor and mentee ever since.

"Dr. Chapman is a warrior fighting health injustice," Jagsi says. "She completely appreciates that social determinants of health far outweigh the influence of factors like medical care. She's drawing her inspiration and strength from individual patient encounters and enriching her work because of them."

Chapman served as a discussant on a panel on workplace inequities at the 2019 American Society of Clinical Oncology's annual meeting in Chicago. She continues her research on whether black women will benefit from different breast cancer screening guidelines since they're diagnosed at a younger age and get more aggressive subtypes.

"I love seeing patients as a radiation oncologist and performing research, and cannot think of a better career to have pursued," Chapman says. "However, when I think about my overarching life goal, it is broader than my career and more about advancing social justice. Research is a means to do that, and continuing to see patients and continually being made aware of the challenges discrimination poses for many in academia drives a lot of the questions I ask." 🌟



Lawlor with Jennifer Jimenez in the lab.

Education at the Rogel Cancer Center

AN ANNUAL RESEARCH TRAINING SYMPOSIUM PROVIDES OPPORTUNITIES FOR TRAINEES TO PRESENT RESEARCH IN PROGRESS. THERE ARE ALSO SEVERAL CELLS-TO-SOCIETY SEMINARS EACH YEAR FOR INVESTIGATORS TO PRESENT HIGH-LEVEL OVERVIEWS OF PRESSING ISSUES IN CANCER RESEARCH, FROM CELL BIOLOGY TO POPULATION SCIENCES. PRESENTERS COVER DIFFERENT PERSPECTIVES ON THE ISSUE.



Reshma Jagsi, M.D., D.Phil., and Christina Chapman, M.D., share an interest in social determinants of health.

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