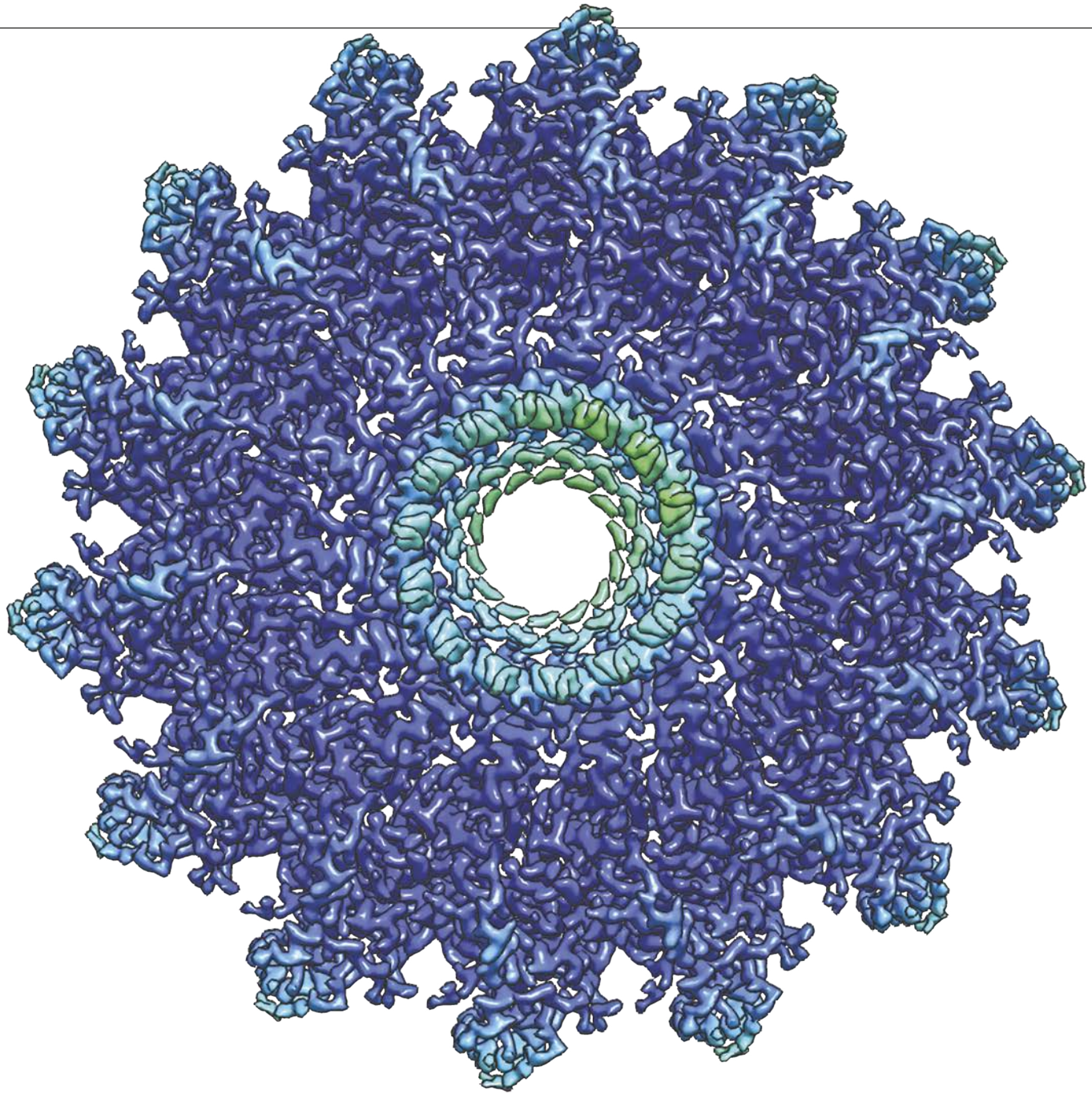
Illuminate

UNIVERSITY OF MICHIGAN HEALTH ROGEL CANCER CENTER 2022



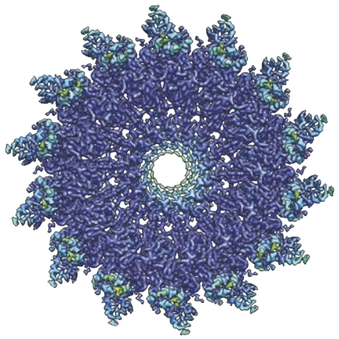
The Cancer Microbiome

Also: Fighting racial disparities in outcomes & promising translational discoveries

ON THE COVER

A cryo-electron microscopy image from the lab of Rogel member Melanie Ohi, Ph.D., reveals part of the complex molecular machinery of Helicobacter pylori's secretion system, which triggers the chronic inflammation that is a major risk factor for stomach cancer.

Bottom view:



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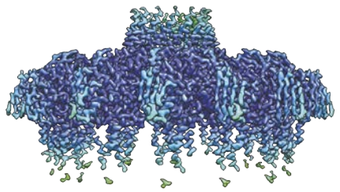

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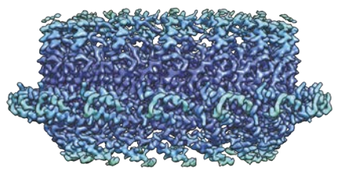

To obtain the images, biochemically purified proteins are flash frozen at -180 degrees Celsius, preserving their natural shape and organization. Then the microscope's electron beam reveals the shape of these nanometer-sized proteins. (A nanometer is about one million times smaller than the tip of a needle.) Raw images are extremely "noisy" and hard to see, so large numbers of images for each sample must be collected. Specialized computer analysis then combines hundreds of thousands of individual, 2D snapshots from different angles into a composite that can be viewed in 3D. Many 3D structures determined by cryo-EM are now at a high enough resolution that researchers can visualize individual atoms.

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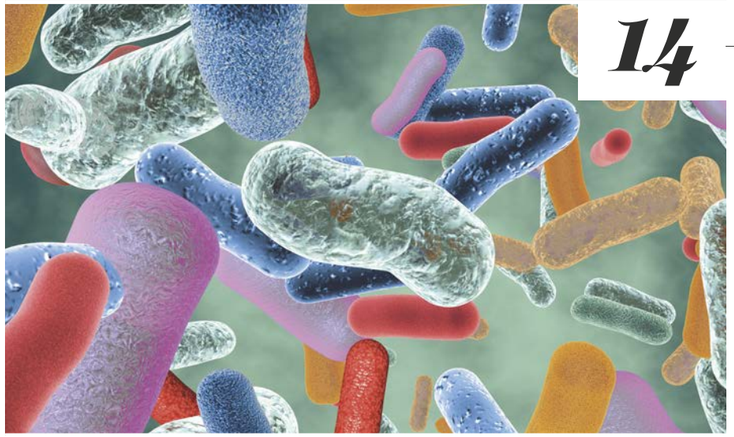

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FEATURES

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9
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48
departments

1,500
annual publications

1,500
yearly clinical trial accruals

$170M
grant funding

No.6
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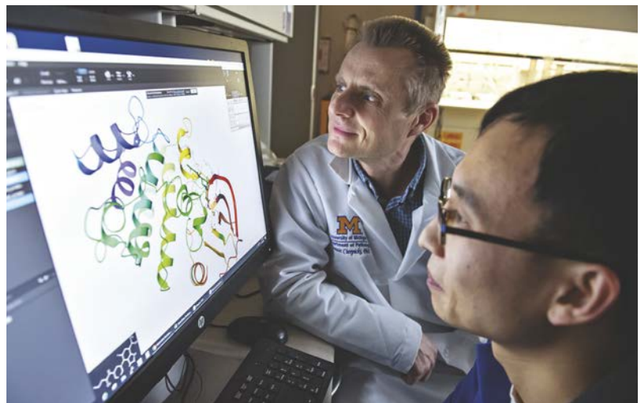


Director's Letter

Dear Colleagues,

Much has changed since the first issue of our research magazine, *Illuminate*, was published in early 2020 — within our cancer center and around the U.S.

Academic medicine, like the rest of the country, is undergoing an awakening about the pressing need to address racial inequities in the wake of the murders of George Floyd, Ahmaud Arbery and others. And the continuing COVID-19 pandemic has starkly underlined racial disparities in health care, including for cancer patients and survivors.

As my colleague, **Dr. Lori J. Pierce**, highlighted in her presidential remarks to the American Society of Clinical Oncology last year, "institutional racism is finally being recognized as a societal plague that is devastating to all of us."

And while all the leaders at the Rogel Cancer Center remain responsible for supporting and promoting efforts to improve diversity, equity and inclusion in their respective areas, we are proud to have **Dr. Erika Newman** as our first Associate Director for Diversity, Equity, Inclusion and Justice. In this newly created role, Dr. Newman will help advance critical diversity-related objectives not just within the center, but also in collaboration with other efforts across Michigan Medicine and the broader University of Michigan campus.

It is appropriate, therefore, that among the topics we're highlighting in this second issue of our magazine is the cancer center's multifaceted efforts to improve equity in health outcomes globally while working to reduce disparities in outcomes in the communities we serve locally, in Michigan and beyond. This is a vital issue and we must draw attention to the need for continued progress.

That's also why the Rogel Cancer Center has made cancer health equity a top strategic research priority for the next five years — bridging efforts to address mechanisms of cancer initiation, progression and resistance; cancer treatment and care delivery paradigms; and cancer risk reduction.

In this issue you'll also read about exciting translational initiatives that originated in our labs — a recognition that while we have an incredibly robust discovery science program, all our work, ultimately, is about improving the lives of patients through innovations in prevention, early diagnosis and treatment.

We also explore the emerging topic of the cancer microbiome — that is, the myriad ways microbes influence the initiation, progression and treatment of cancer, and which cancer center members from across the breadth of the university are investigating from a host of angles.

In these pages, we also share some of our most exciting research discoveries of the past year — which range from explaining why patients whose cancer spread to the liver have worse outcomes to the development of first-in-class inhibitors against a key leukemia protein. **Dr. Max Wicha**, a luminary in the field of stem cell biology and our former director, reflects on half a century of research advancements. And we profile some of the amazing talent among our junior faculty and trainees, because a top goal remains to train the next generation of pioneers in the cancer field.

The past couple of years have been difficult and heartbreaking for so many in our communities and around the world. I have been awed and inspired, however, by the exceptional efforts and resilience of our staff, faculty, and trainees, and the patients and families we serve.

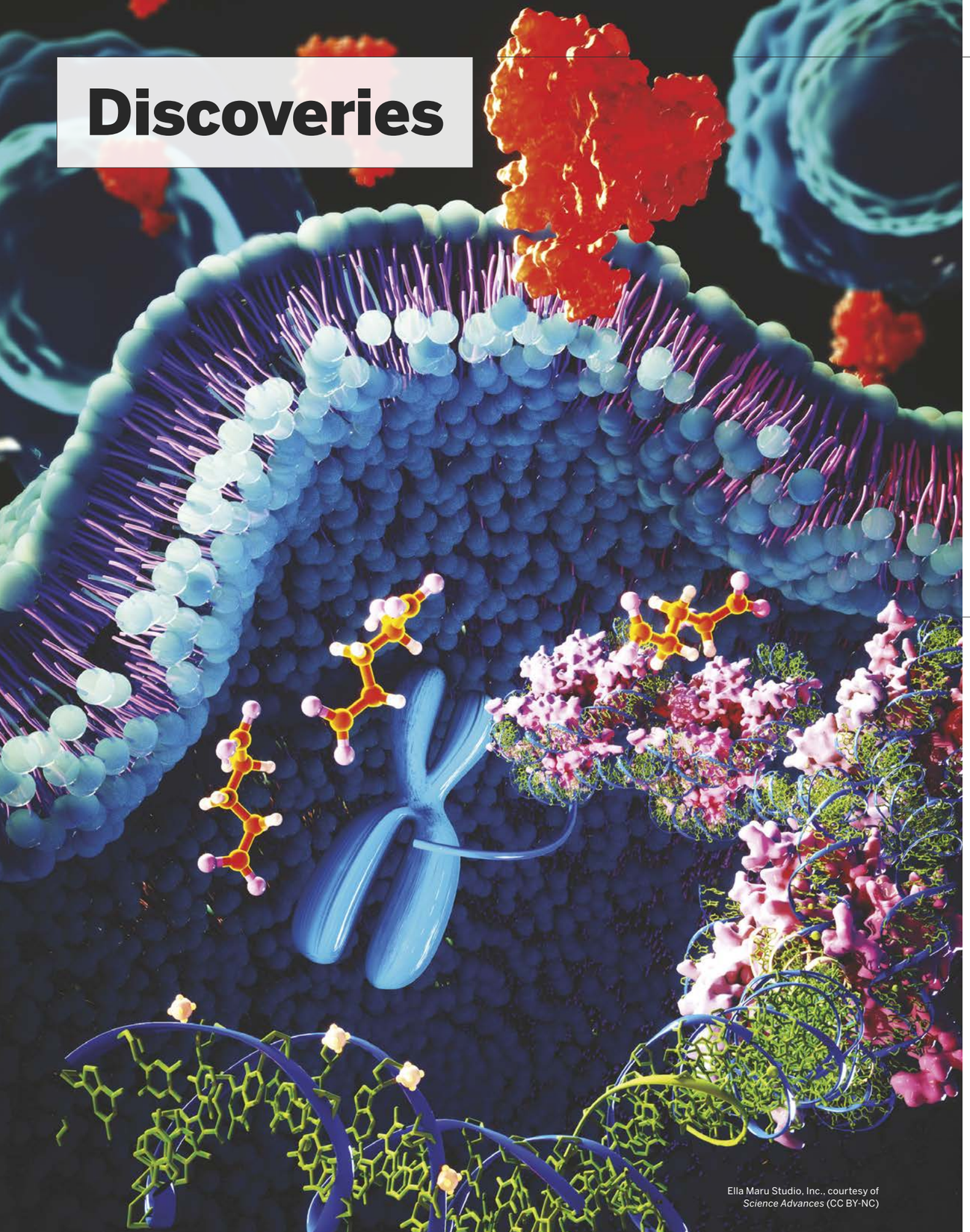
Moreover, I have never been more proud and excited about the achievements, and potential for further major impact, of our research enterprise. Rogel members continue to explore and expand our fundamental understanding of cancer at the same time as we strive to make truly meaningful improvements in the lives of those affected by the disease.

Sincerely,

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

Photo: Erica Bass

Discoveries



Ella Maru Studio, Inc., courtesy of *Science Advances* (CC BY-NC)

Subtype May Hold the Secret to the Success of Glioma Immunotherapies

NOVEL TREATMENTS ↔ A single common genetic mutation may hold the key to making immunotherapy more effective against gliomas, according to new mouse model findings from the labs of **Maria Castro, Ph.D.**, and **Pedro Lowenstein, M.D., Ph.D.**

The flip of a single amino acid from arginine to histidine in a subset of these brain and nervous system tumors sets off a series of changes that sensitizes them to treatment with immune-stimulating therapy to which they would otherwise be largely resistant.

Having discovered this sensitivity and mapped the underlying mechanisms, the research team identified a blood growth factor secreted by tumors harboring the mutation — one already used to stimulate the production of white blood cells and reduce the risk of infection in patients receiving chemotherapy — that holds promise for making treatments against gliomas more effective.

"It's been known for about a decade that patients with low-grade gliomas that have this IDH1 mutation have a much longer median survival," says Castro, a professor of neurosurgery and cell and developmental biology. "We set out to try to understand why, and to see if there were any differences that could be harnessed to improve outcomes more broadly."

In a mouse model of glioma without the IDH1 mutation, administering G-CSF, the blood growth factor produced by their mutant cousins, more than doubled median survival times. When immunotherapy was also added, the effect was even more profound, the team reported in *Science Advances*.

Even low-grade gliomas are uniformly fatal, eventually coming back after treatment with some combination of chemotherapy, radiation and surgery.

"It's an inescapable destiny, so we really need new therapies," Castro says.

Score Predicts Kidney Cancer Path

BIOMARKERS ↔ A retrospective study in patients with localized renal cell carcinoma found that a biopsy-based cell cycle proliferation score could help with clinical risk stratification.

While active surveillance is a potential option for patients with lower-grade tumors, the risk of missing high-grade disease has limited its use. Gene expression classifiers, such as those based on cell cycle proliferation markers, have been used in other cancers.

When added to a baseline model for kidney cancer that includes age, sex, race, lesion size, biopsy grade and histology, high cell cycle score was significantly associated with poorer outcomes, a U-M-led team including **Rohit Mehra, M.D.**, **Todd Morgan, M.D.**, and **Jeremy Taylor, Ph.D.**, reported in *European Urology*.

Rogel findings help show why patients with mutant IDH1 gliomas survive longer, paving the way toward improved immunotherapies.

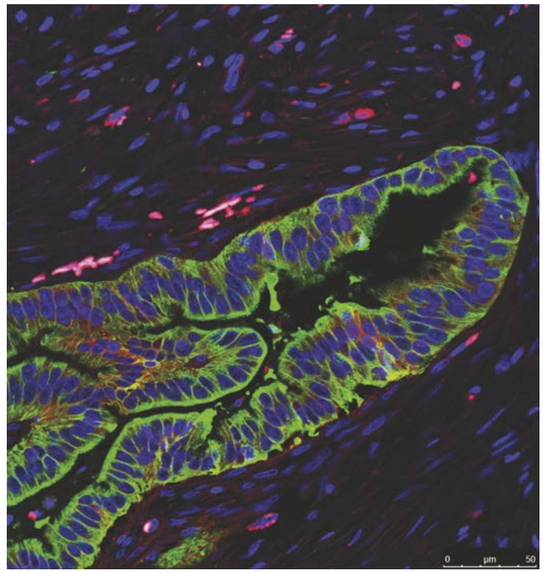
Ovarian Cancer End-of-Life Care More Aggressive for Minorities

DISPARITIES ↔ People with ovarian cancer frequently receive aggressive end-of-life care despite industry guidelines that emphasize quality of life for those with advanced disease, a team led by first author **Megan Mullins, Ph.D., M.P.H.** (right), and co-senior author **Lauren Wallner, Ph.D.**, found.

By 2016, ICU stays and emergency department visits in the last month of life had become more common for people with ovarian cancer than they were in 2007, the earliest year from which researchers analyzed data. The proportion of non-Hispanic Black people who turned to the emergency department for care was even higher — double that of non-Hispanic whites. Black people were also nearly twice as likely to undergo intensive treatment, including life-extending measures such as resuscitation or the insertion of a feeding tube, the group reported in *Cancer*.

"Guidelines and recommendations are not making enough of a difference in the type of care people with ovarian cancer receive at the end of their lives, especially for people of color," Mullins says.

Mapping the Immune Landscape in Pancreatic Cancer



Rogel researchers implemented a multimodal approach to elucidate the immune landscape in pancreatic cancer cells.

TUMOR MICROENVIRONMENT ↬ Rogel researchers combined single-cell RNA sequencing with two other investigative techniques to create what is believed to be the most robust and detailed portrait to date of the network of interactions that suppress the body's immune response in and around pancreatic tumors.

The team's findings, which appeared in *Nature Cancer*, spotlight the degree to which immune response varies from patient to patient and tumor to tumor — which will need to be taken into account as new immunotherapy combinations are developed against the deadly disease.

"Pancreas cancers just have not been sensitive to immune therapy, and those of us in the field are trying to sort out why that is, what makes this cancer so different," says study senior author **Marina Pasca di Magliano, Ph.D.** "What has been lacking is even a basic understanding of the variety and individual differences in immune response between patients."

Why Patients with Liver Metastases Have Worse Outcomes

IMMUNOTHERAPY ↬ Liver metastases diminish the effectiveness of immunotherapy in both patients and preclinical models. And patients whose cancer has spread to their livers derive limited benefit from immunotherapy independent of other biomarkers of response, a Rogel-led team reported in *Nature Medicine*.

A multidisciplinary team led by **Michael Green, M.D., Ph.D.**, and **Weiping Zou, M.D., Ph.D.**, looked at data from 718 patients who had received immunotherapy at U-M. Patients had a variety of cancer types, including non-small cell lung cancer, melanoma, urothelial cancer and renal cell cancer, which had spread to different organs, including the liver and lungs.

Repeatedly, those with liver metastases had worse responses to immunotherapy. The issue was not just in the liver either: these patients had more cancer throughout their bodies, compared to similar patients whose cancer had spread but not to the liver.

"The liver is initiating a systemic immunosuppressive mechanism. The mechanism happens in the liver, but we see the systemic impact throughout the body," Zou says.

Coupling immunotherapy with radiotherapy to the liver in mice, however, restored the immune cell function and led to better outcomes — suggesting a potential path forward.

"With these promising results, we are now looking to open clinical trials in this space to better understand the mechanisms at play in human tumors," Green adds.

Improving Esophageal Cancer Screening

EARLY DETECTION ↬ A large, community-based, longitudinal population study independently validated four tools for predicting adenocarcinomas of the esophagus and esophagogastric junction — finding all four appeared to be superior to using gastroesophageal reflux disease (GERD) alone for risk stratification.

Following up on the study, which appeared in the *American Journal of Gastroenterology*, lead author **Joel Rubenstein, M.D.**, is working with interdisciplinary cancer care delivery researchers to adapt the tools for use with the electronic health record and implement a point-of-care screening tool to increase the uptake of upper endoscopies in high-risk patients.

Photo: Nina Steele, Ph.D.

Joshi Alumkal, M.D., led work to target lineage plasticity in advanced prostate cancer.

Targeting Lineage Plasticity with BET Inhibitors

NOVEL APPROACHES ↬ A team of researchers led by **Joshi Alumkal, M.D.**, uncovered new mechanisms underlying an important type of resistance in treatment-resistant prostate cancers called lineage plasticity. This resistance mechanism causes these cancers to undergo a deadly identity switch — shifting from resembling glandular cells to neuroendocrine cells, which can behave more like small cell lung cancer.

Appearing in *Clinical Cancer Research*, the team's findings outline a promising path to overcoming this resistance: BET bromodomain inhibitors. These compounds work against bromodomain and extra-terminal (BET) proteins, which are involved in activating genes.

"We know that treatment-emergent neuroendocrine prostate cancer is becoming more frequent as we use new and more potent androgen receptor inhibitors," Alumkal says. "Our prior work examining patients progressing on these newer androgen receptor inhibitors demonstrated that neuroendocrine prostate cancer was found in 17% of cases. By comparison, we find it in less than 1% of patients who have not undergone any form of androgen receptor inhibition. This strongly suggests that interference with androgen receptor function contributes to the increased numbers of treatment-emergent neuroendocrine prostate cancers we now see clinically."

Turning Cold Prostate Tumors Hot

IMMUNOTHERAPY ↬ A Rogel-led study in *Nature Cancer* revealed that targeting the lipid kinase PIKfyve with a multi-tyrosine kinase inhibitor could turn advanced prostate tumors from "cold" to "hot" through inhibition of autophagy. This may prime the tumor immune microenvironment and be an effective treatment strategy alone or in combination with immunotherapies, the team led by **Arul Chinnaiyan, M.D., Ph.D.**, reported.

Based on the findings, researchers have begun phase 2 clinical trials using the identified inhibitor, ESK981, alone or in combination with the immunotherapy nivolumab.

Photo: Leisa Thompson

ACA Lowered Financial Burden on Survivors Under 65

ACCESS TO CARE ↬ Cancer survivors between 18 and 64 faced fewer financial barriers to health care after the Affordable Care Act was implemented than they did before the landmark law took effect, according to a study led by first author **Christopher Su, M.D.**, and senior author **Susan Goold, M.D.**, in *JCO Oncology Practice*. In fact, the ACA helped the financial burden for survivors under 65 fall to its lowest estimated level in 20 years.

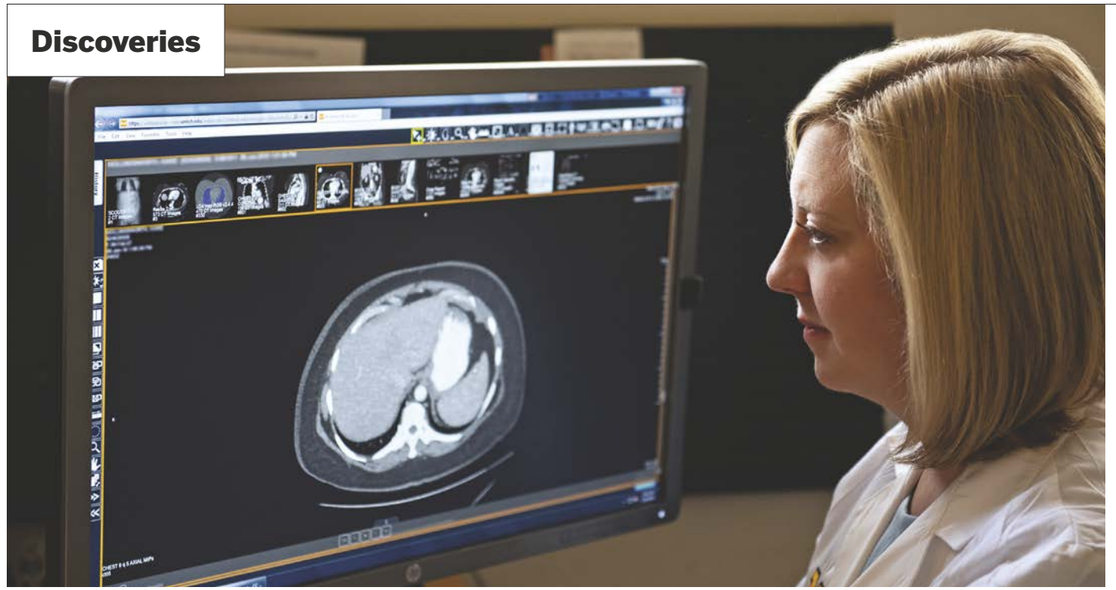
"There has been a lot of talk about the ACA affecting people who don't have the Medicare safety net," says Su, a hematology/oncology clinical fellow. "We were able to drill down and show that it did make a difference to these younger cancer survivors."

Similar Factors Behind Disparities in Cancer, COVID-19

DISPARITIES ↬ Income level, employment, housing location, medical insurance, education, tobacco and alcohol use, diet and obesity, access to medical care. These are some of the factors causing worse cancer outcomes in people who are Black. The same factors are also causing worse outcomes from COVID-19 in this population.

"The similarities between COVID-19 issues and cancer disparities is uncanny," says **John Carethers, M.D.**, who co-authored a study in *Clinical Cancer Research* that outlined these parallels and recommended policy changes and strategies to improve outcomes.

"In cancer we are seeing in slow motion what has been observed rapidly with COVID — that the same conditions in our society put specific groups at risk for both. If we can fundamentally change socioeconomic inequality, we theoretically could reduce disparities in both diseases," Carethers adds.



Erin Cobain, M.D., and colleagues found next-generation sequencing improved outcomes for cancers with unknown tissue of origin.

How Useful is Next-Generation Sequencing for Patients with Advanced Cancer?

PERSONALIZED MEDICINE ↔ A study of more than 1,000 patients seen at the Rogel Cancer Center suggests next-generation sequencing can significantly influence clinical care and improve outcomes — especially for certain subsets of patients.

The findings, which appeared in *JAMA Oncology*, showed that potentially actionable genomic alterations were found in nearly 80% of patients. And of the 130 patients who received sequencing-directed therapy, nearly 40% experienced some clinical benefit, with 20% experiencing exceptionally good responses — defined as keeping their disease under control for at least one year.

Moreover, for patients with cancers of unknown origin, sequencing was able to decode the tissue of origin for the cancer in half of cases — giving doctors much better clues about what standard therapies, as well as targeted therapies, might help.

One of the most telling results of the study was that potentially inheritable cancer risk was identified in 16% of patients, says study first author **Erin Cobain, M.D.**

Liquid Biopsy Could Signal Treatment Failure

BIOMARKERS ↔ A sensitive blood test being developed by a Rogel-led team shows promise for predicting months earlier than standard imaging scans whether metastatic HPV-positive throat cancer will respond to treatment. That's according to a study, published in *Oncotarget*, validating the test in a small group of patients with metastatic human papillomavirus-related oropharyngeal squamous cell carcinoma.

The group, led by senior authors **Muneesh Tewari, M.D., Ph.D., Paul Swiecicki, M.D.**, and **J. Chad Brenner, Ph.D.**, found that increasing levels of HPV-positive circulating tumor DNA after a course of treatment were a strong indicator that the cancer was not responding to treatment. And that the increasing tumor DNA could be detected months ahead of tumor growth that can be measured on imaging scans.

Single-Cell Sequencing Sheds Light on Chemo Response

CANCER DETERMINANTS ↔ Using single-cell RNA sequencing, a Rogel-led team showed for the first time how individual cells within a single population of cancer cells respond differently to chemotherapy. The responses fell into three groups, activating genes that control cell death, cell division or stress response, according to findings published in *Cell Reports*.

"Collectively, we observed that cells with different fates actually had completely distinct sets of activated genes and that these different 'transcriptomic landscapes' dictate the fates of cells after DNA damage from chemotherapy," says study co-senior author **Jun Hee Lee, Ph.D.**

Photo: Leisa Thompson

Memory T cells Persist in Melanoma Patients with Durable Immunotherapy Response

IMMUNOTHERAPY ↔ Immunotherapy researchers at Dartmouth and U-M discovered how memory T cells are generated in melanoma survivors with vitiligo, and are able to function for years after a tumor is gone.

"We knew we had this group of patients who did better, who survived longer," co-senior author **Christina Angeles, M.D.**, says. "We wanted to better understand and demonstrate why that was the case."

The findings, which appeared in *Nature Cancer*, identified a new subset of "resident memory" T cells that localize to patient skin and tumors, and make high levels of the cytokine interferon gamma. These cells have a unique gene expression profile found in melanoma tumors, from patients who have survived longer than those who don't have the signature. T cells that infiltrate tumors have matching clonal partners that persist in patient skin and blood up to nine years later. No prior study has demonstrated cellular evidence of such long-lived immunity to cancer.

Expanded Lung Cancer Screening Eligibility Would Save Lives

EARLY DETECTION ↔ Reducing the initial screening age and including those with lower smoking exposures would help avert lung cancer-related deaths, according to a study by the Cancer Intervention and Surveillance Modeling Network, led by Rogel's **Rafael Meza, Ph.D.**

The modeling study, commissioned by the U.S. Preventive Services Task Force and published in *JAMA*, looks at the benefits and harms associated with various low-dose computed tomography screening strategies — identifying those that result in the most benefits for a given level of screening. It found that new guidelines would help address current gender and race/ethnicity disparities.

The study suggests that screening individuals aged 50-80 who have a history of smoking a pack of cigarettes every day on average for at least 20 years would result in more benefits than previous criteria, and fewer disparities in screening eligibility by gender and race/ethnicity.

Photo: Nicole Haley

Sriram Venneti, M.D., Ph.D., (left) and team are investigating new approaches against pediatric brain cancer.

New Potential Approach Against DIPG

NOVEL APPROACHES ↔ Progress against DIPG is usually a game of inches. Studies that hint at even small gains are cause for celebration.

That's why Rogel researchers and their collaborators are excited about discoveries that point toward a new potential treatment approach — one that significantly lengthened survival times in mouse models of the brain tumor.

The team's findings, which appeared in the journal *Cancer Cell*, suggest that simultaneously targeting two energy-production pathways within the cancer cells could help overcome the effects of a cancer-causing mutation that is one of the hallmarks of DIPG and similar tumors.

Inhibiting each of the two metabolic pathways individually provided a small increase in how long the mice survived, while targeting both pathways at the same time caused the mice to live much longer.

"Treatments for DIPG are desperately needed. So, while these are still early stage, pre-clinical results, we are excited about continuing to develop this new strategy toward human clinical trials," senior study author **Sriram Venneti, M.D., Ph.D.**, says.

Methionine Critical to Immune Evasion

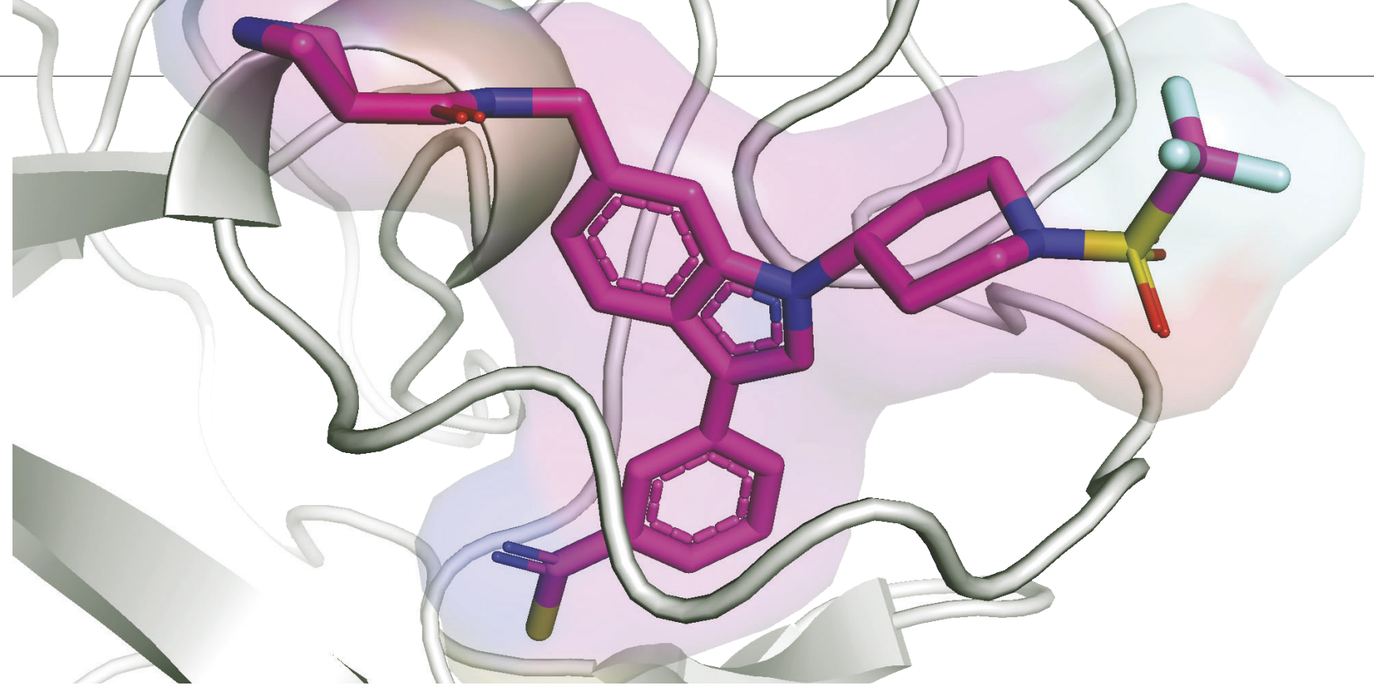
IMMUNOTHERAPY ↔ Targeting methionine signaling in tumor cells may make immunotherapy effective against more cancers, **Weiping Zou, M.D., Ph.D.**, and colleagues reported in *Nature*. The findings identified a mechanistic connection between methionine metabolism, histone patterns and T cell immunity in the tumor microenvironment.

Methionine has a significant impact on T cell survival and function. T cells with low levels of methionine become abnormal. Low methionine in the T cells also alter histone patterns that cause T cells to be impaired.

Tumor cells and T cells fight for methionine — with tumor cells taking the amino acid from T cells over and over, and rendering them ineffective. Supplementing methionine can actually improve T cell function, according to the study, which spanned multiple Rogel labs. And because tumor cells have more transporters that deliver methionine, impairing those transporters resulted in healthier T cells.

Meanwhile, Zou was awarded a $3.2 million grant from the National Cancer Institute to advance the work.

Weiping Zou, M.D., Ph.D., led several notable immunotherapy studies last year.



X-ray crystallography shows an ASH1L inhibitor developed at U-M in complex with the protein. The drug discovery effort was led by the labs of Jolanta Grembecka, Ph.D., and Tomasz Cierpicki, Ph.D.

First-in-Class Inhibitors Against Key Leukemia Protein

NOVEL APPROACHES ↔ A team of researchers led by **Jolanta Grembecka, Ph.D.**, and **Tomasz Cierpicki, Ph.D.**, has developed first-in-class small molecules to inhibit ASH1L's SET domain — preventing critical molecular interactions in the development and progression of leukemia. To date, ASH1L has been challenging to target therapeutically.

The team's findings, which used fragment-based screening, followed by medicinal chemistry and a structure-based design, appeared in *Nature Communications*. In mouse models of mixed lineage leukemia, the lead compound, AS-99, successfully reduced leukemia progression.

Dual-Eligible Patients Get Better End-of-Life Care at Cancer Centers

ACCESS TO CARE ↔ Patients who were eligible for both Medicaid and Medicare received better end-of-life care at cancer centers and integrated delivery networks, Rogel-led research found.

Dual-eligible patients in these health settings experienced superior outcomes across most of the quality measures assessed. They were more likely to enroll in hospice in their last month of life and less likely to die in a hospital setting, **Lindsey Herrel, M.D.**, **David C. Miller, M.D.**, and colleagues reported in *Cancer*.

A possible explanation for the differences could be that cancer centers and integrated networks are better able to assess patient preferences when it comes to care at the end of life, Herrel notes. Going forward, a crucial step will be facilitating more of these critical conversations, regardless of the setting, she adds.

Imaging Features Promising for Predicting HPV-Associated Head and Neck Cancer Outcomes

BIOMARKERS ↔ Pre-treatment features from standard-of-care PET and CT imaging show promise for predicting long-term outcomes in patients with HPV-associated oropharynx cancer, senior author **Michelle Mierzwa, M.D.**, and team reported in *Radiotherapy and Oncology*.

The study, which is the largest to date of patients uniformly treated with chemoradiotherapy, suggests that PET and CT features could play a crucial role in determining treatment intensification and de-escalation.

A New, Vital Player in GVHD

BIOMARKERS ↔ A long noncoding RNA whose function was previously unknown turns out to play a vital role in mobilizing the immune response following a bone marrow transplant or solid organ transplantation.

This RNA molecule, Linc00402, helps activate T cells in response to the presence of foreign human cells, according to findings published by senior study author **Pavan Reddy, M.D.**, and collaborators in *Science Translational Medicine*. Furthermore, Linc00402 was decreased in T cells from patients who developed graft-versus-host disease after hematopoietic stem cell transplantation.

The investigation, which included samples from more than 50 patients who underwent a bone marrow or heart transplant, suggests inhibiting the RNA therapeutically might improve outcomes for transplant recipients.

Pembro Helps Those with Metastatic Breast Cancer and High Mutational Burden

IMMUNOTHERAPY ↔ The immunotherapy agent pembrolizumab can provide clinical benefit to some patients with metastatic breast cancer whose tumors were found to have a high number of mutations, and whose cancer continued to progress with standard treatments.

That's according to results from ASCO's Targeted Agent and Profiling Utilization Registry (TAPUR) study. The findings appeared in the *Journal of Clinical Oncology*.

The goal of TAPUR is to use next-generation genomic sequencing data to assess whether cancer drugs previously approved in one cancer type might benefit additional groups of patients across cancer types due to specific alterations to DNA and RNA in their tumors.

"Immunotherapy doesn't work for every patient, but when it does work, it can have really profound effects," says study lead author **Ajjai Alva, MBBS**, principal investigator for the U-M trial site. "When it comes to a biomarker to tell us which patients will respond best to immunotherapy, we still haven't found the perfect marker, the holy grail — but we have found a very good candidate biomarker in high tumor mutational burden."

Photo: Edda Pacifico

The Cancer Microbiome

Scientists are just starting to appreciate the many ways microbes influence the initiation, progression and treatment of cancer. Here's what Rogel researchers are learning.

By Sarah Kearns, Ph.D., and Ian Demsky

In 2016, a group of scientists publishing in *PLOS Biology* estimated that our bodies contain not the commonly accepted 10 human cells for every one microorganism, but something closer to a 1-to-1 ratio — with these tiny counterparts collectively weighing 4 or 5 pounds.

This "other half" of us plays a vital role in human health, with symbiont communities thriving on our skin, and in our mouths, noses, lungs, digestive tracts and a host of other organs. And researchers are just starting to probe the multiplicity of roles these organisms can play in the initiation, progression and treatment of cancer.

This new appreciation has led to growing efforts at the University of Michigan Health Rogel Cancer Center, and elsewhere around the globe, to harness the power of the microbiome to prevent cancer and improve therapies.

"*H. pylori* don't want to give anyone stomach cancer," says **Melanie Ohi, Ph.D.**, a professor of cell and developmental biology. "They're just trying to create a niche to live in."

Over the last several years, Ohi's lab at the U-M Life Sciences Institute has used cryo-electron microscopy to capture, in increasing detail, near atomic-level 3D snapshots of the molecular machinery that *Helicobacter pylori* uses to infect host cells, triggering the chronic inflammation that can lead to the development of gastric cancer.

While roughly half the human population has been colonized by the bacterium, most people never experience any ill effects. Still, *H. pylori* infection is the strongest known risk factor for stomach cancer, which is the fourth-most deadly type of cancer worldwide, according to the World Health Organization.

Ohi's team and their collaborators published the best views to date of the bacterium's secretion system in *eLife*, revealing two species-specific components, and greatly improved resolution of its spokes and outer ring. (From the top, the squiggly proteins of this core complex look like a spaghetti mandala, and the fully assembled sideview resembles a mechanical mushroom cloud.)

Ohi likens this structural biology approach to developing a schematic of the inside of a lock to figure out the exact size and shape of the key you need.

"By understanding how these molecular machines move, how each part of the secretion system functions, our goal is to find new ways to target the processes that cause disease," she says.

Forests and trees

One of the challenges for studying the relationships between our microbiomes and cancer is that they're both varied, dynamic and complex systems in their own rights.

Plus, there's no one-size-fits-all microbiome. Individuals can have healthy, stable populations of gut bacteria made up of different species due to factors including inheritance, geographic location and diet.

"You can have many different ecosystems that could be considered to be healthy. A jungle in the Amazon can be just as healthy and productive as a redwood forest," says **Vincent B. Young, M.D., Ph.D.**, a professor of internal medicine and of microbiology and immunology, whose lab studies the microbial ecology of gastrointestinal infections.

Moreover, the complexities of interactions between microbes and hosts are staggering, he notes. Bacteria that have co-evolved with humans can play both detrimental and positive roles in different aspects of health. For example, testing for and treating *H. pylori* is of clear benefit for lowering the incidence of stomach cancer. At the same time, infection with the bacterium has also been associated with *reduced* risk for asthma, inflammatory bowel disease and acid reflux, which is in turn a risk factor for esophageal cancer.

Accordingly, a multidisciplinary approach is needed — one that brings together expertise in microbial ecology, immunology, cancer cell biology and computational biology, Young and co-authors including cancer center member **Thomas Schmidt, Ph.D.**, argue in a 2020 *Trends in Cancer* editorial.

Melanie Ohi, Ph.D., (right) uses cryo-electron microscopy to study bacterial secretion systems that can ultimately lead to stomach cancer.

"Each cancer is itself an ecosystem in which cancer cells interact with each other and with stromal cells in intricate, dynamic ways," the authors write. "Common factors such as circulating metabolites, systemic immunity, etc. can impact on — and be affected by — the two types of ecosystems simultaneously. The relevant links between microbiomes and cancers may be impossible to reduce to a single component."

These interactions can be both cooperative and competitive, notes **Yatrik Shah, Ph.D.**, a professor of molecular and integrative physiology and of internal medicine.

"A tumor is a very needy accumulation of cells," says Shah, who studies gastrointestinal homeostasis, inflammation and cancer. "It takes up nutrients, many of which the microbiome would rather be using. So, that forces the microbiome to adapt."

As cancer develops, it changes the abundance of particular species of bacteria within its environment, often reducing populations of beneficial bacteria, he says. Then, once the tumor has established itself and altered the microbiome to its liking, the bacteria that are left are likely to be complicit in tumor growth and even promote cancer progression.

"It really remakes its environment to suit its own needs," Shah says.

Patrick Schloss, Ph.D., a professor of microbiology and immunology, has also been studying these dynamic interactions — especially the impact that perturbations of the microbiome can have on human health, including the development of cancer.

One area his group has focused on is oral microbes' contribution to tumor growth in colorectal cancer.

People with colon cancer often have populations of bacteria in their gut that are typically found solely in the mouth — organisms like *Fusobacterium nucleatum* and species of *Porphyromonas*.

"Even though healthy individuals are swallowing saliva every day, you won't see these populations in their gut," Schloss says. "So, there's something interesting going on with their relationship to colorectal cancer."

The conditions for tumor initiation in colon cancer depend less on any single factor — individual bad microbial actors, specific bacterial virulence factors, disruption of signaling pathways, or promotion of

Photo: Leisa Thompson

inflammation — than on all of these components working in concert, he says.

And then added into this mix are the uniquely stubborn properties of oral microbe colonies when they glom together in sticky matrices called biofilms.

"Big picture: This means that as scientists are designing new studies, creating screening tests based on the microbiome, or developing new therapeutic interventions, we really need to be taking the entire microbial community in and around tumors into consideration rather than just zeroing in on individual pathogens," says Schloss, whose group is also interested in the role of virus communities — or the virome — in the development of colorectal cancer, largely through their modulation of bacterial communities.

Different bacteria, different levels of cancer

Identifying specific members of the gut microbiome that contribute to the development of cancer is challenging because of the natural variation in microbial communities between individuals, says **Grace Chen, M.D., Ph.D.**, an associate professor of hematology/oncology.

Scientists have found significant differences between the bacteria found in patients with colorectal cancer and those without, but it has been difficult to reach strong conclusions about causation because of the natural dissimilarities between one person and another and the lack of longitudinal studies, she says.

To overcome this hurdle, Chen uses specialized mouse models — either developed to lack any microbial communities or colonized by only specific bacteria — to study how the host immune system and the gut microbiome affect intestinal inflammation and the development of cancer.

"In controlled mouse studies, we were able to demonstrate specific changes to the microbiome during the development of inflammation and tumors, and that these changes directly cause disease," adds Chen, who frequently collaborates with Schloss.

Several recent studies from her lab showcase just how powerful these changes can be.

For example, different microbiomes can be associated with different levels of immune cell stimulation, specifically CD8+ T cells, Chen's group found. And while these T cells normally help protect the body against cancer, overstimulating them can potentially promote inflammation and exhaust the T cells — which can actually increase susceptibility to cancer, according to findings they published in *Cell Reports*.

Grace Chen, M.D., Ph.D., and Pavan Reddy, M.D., discuss a research project.

Photo: Leisa Thompson

"There has also been a lot of excitement about the role bacteria may play in improving the effectiveness of immunotherapy by promoting T cell activation," Chen says. "This work suggests it may be a double-edged sword — and that in the context of an unhealthy microbiome, the promotion of T cell exhaustion is something researchers need to watch out for."

In cancer patients, disruption of the healthy gut microbiome has been associated with poorer responses to treatment with immune checkpoint inhibitors, so there has been keen interest in making targeted adjustments to improve outcomes.

Chen's findings grew out of experiments that showed the powerful influence of the microbiome in the development of cancer when genetics are taken out of the picture.

Starting with two groups of genetically different mice, each with distinct microbiomes, they found that the one group fared better than the other when exposed to the same carcinogen.

Then the team ran another experiment, transplanting the microbiomes from each group of mice into two new, genetically identical colonies of germ-free mice. Again, mice who shared bacteria with the original second colony developed more tumors.

"This showed that the composition of the gut microbiota can directly influence tumor development," Chen says. The team also identified specific bacteria that consistently correlated with more tumors — findings which will need to be further validated.

Chen's team next conducted experiments to better understand what was driving the increased inflammation and tumor growth. Through immune cell profiling, they found that there were more T cells in the colon tissue of mice with bacteria from the second colony, and many more CD8+ cells.

"It's a little counterintuitive, since T cells and CD8+ cells are usually associated with better outcomes in colorectal cancer patients," Chen says. "We hypothesize that these cells get over-activated in the presence of certain bacteria and then exhausted, leaving them less capable of killing tumor cells."

Bridging bench and bedside

Scientists are just starting to understand the ways good and bad gut microbes adapt as healthy conditions shift toward disease.

A team led by **Kathleen Cho, M.D.**, the Peter A. Ward Professor of Pathology and director of gynecologic pathology at U-M, recently investigated the influence

A Sherman lab dive

Photo courtesy of the U-M Life Sciences Institute

Drugs from Nature's Pharmacy

WHILE OTHER SCIENTISTS work to better understand the complex interactions between bacteria and their human hosts, Rogel Cancer Center member **David H. Sherman, Ph.D.**, looks to tap into the rich biochemistry that has evolved inside microbes to pioneer new anti-cancer drugs and other medicines.

Sherman, the Hans W. Vahlteich Professor of Medicinal Chemistry at the College of Pharmacy, has conducted diving expeditions and trips to remote locations around the globe to collect rare bacteria that might harbor the next big breakthrough.

"Symbiotic microbes have long been thought to be the true sources of many of the natural products that have been isolated from invertebrates in the ocean and on the land — but very little is known about them because it's extremely difficult to identify them and culture them in the lab," Sherman says.

A few years ago, for example, Sherman's group pinpointed the true origins of an anti-cancer compound known as ET-743, or trabectedin, which had originally been harvested from a type of sea squirt. By analyzing the genome of this mangrove tunicate along with the microbes that live inside it, the team was able to isolate the genetic blueprint of ET-743's producer — a bacterium known as *Candidatus* Endoecteinascidia frumentensis.

"Currently, many of these compounds can only be harvested in small amounts from host animals, which is unsustainable from an economic and environmental perspective," says Sherman, who also holds appointments at the U-M Life Sciences Institute, Medical School and College of Literature, Science, and the Arts. "Our hope is that understanding the genomes of these microorganisms and the chemical reactions that occur inside them will provide new avenues to economical and sustainable production of the medicinal molecules they make."

A 3D view of the complex molecular machinery *H. pylori* use to infect cells.

of the microbiome on the development of ovarian cancer and related cancers of the upper genital tract in a mouse model of high-grade serous carcinoma.

Half of the mice in the study were given antibiotics, which changed the composition of the bacteria in their digestive and reproductive tracts. Compared to control mice, the treated mice developed significantly fewer tumors and their cancer was less advanced at the end of the study period, according to findings that the group published in *Cancer Research*.

"This is a close model of human ovarian cancer, and our findings suggest that the microbiome does influence its pathogenesis," Cho says. "This model system could be used to explore whether manipulating the microbiome could improve ovarian cancer's generally poor response to immunotherapies."

Meanwhile, **Nobuhiko Kamada, Ph.D.**, an associate professor of internal medicine, has been investigating how intestinal inflammation actually reprograms the metabolic pathways of gut bacteria such as *E. coli*, allowing them to thrive in changing environments. Over time, chronic inflammation and related immune changes in the gut can promote the development of cancer.

"We found that in the inflamed gut, *E. coli* shifts its metabolism to make use of the amino acid L-serine to maximize its growth potential," says Kamada, whose lab focuses on how the gut microbiome and host immunity influence gastrointestinal health and disease.

"Maintaining a healthy gut microbiome nurtures our immune system so that our immune cells can effectively fight against cancer."

Kai Han, Ph.D

Withholding amino acids from the diet, particularly L-serine, blunted inflammation-induced *E. coli* growth in mouse models — and did so without disrupting the host immune response, his group recently reported in *Nature Microbiology*.

"Our findings suggest dietary interventions to influence nutrient availability could help against diseases driven by disruptions of the healthy gut microbiome — like inflammatory bowel disease, which is a major risk factor for cancer," he says. "They also point toward L-serine utilization pathways as potential therapeutic targets to inhibit the growth of certain pathogenic bacteria without harming beneficial bacteria."

Kamada and Chen were also collaborators on an effort led by **James Moon, Ph.D.**, the John G. Searle Associate Professor of Pharmaceutical Sciences at the U-M College of Pharmacy, to develop a dietary fiber gel that holds promise for improving the potency of immunotherapies against cancer.

"It's amazing to think that something as simple and safe as eating more of a dietary fiber like inulin could make such a big difference," Moon says.

Inulin, a fiber found in chicory root, Jerusalem artichoke and other plants, is a prebiotic that provides a rich source of nutrients to beneficial microbes, helping them to proliferate.

"Importantly, the benefits go beyond colon cancer," he notes. "The changes in the gut microbiome stimulate T cells, which circulate throughout the body amplifying the activity of immunotherapy treatment."

The inulin gel improved immune checkpoint inhibitor therapy in mice with skin cancer as well as those with colon cancer, the group reported in *Nature Biomedical Engineering*.

Additionally, inulin was approved by the Food and Drug Administration in 2018, which will shorten the hurdles of moving the findings in mouse models into human clinical studies, Moon adds.

"We and others have shown that the gut microbiome has a crucial role in our immune responses," notes study first author **Kai Han, Ph.D.**, a postdoctoral fellow in Moon's lab. "Close to 70% of lymph nodes in our bodies are located in the gastrointestinal tract and, therefore, microbes residing in the gastrointestinal tract closely interact with our immune cells. Maintaining a healthy gut microbiome nurtures our immune system so that our immune cells can effectively fight against cancer."

And that's not the only place Rogel researchers are looking to leverage the microbiome in the clinic.

A group of investigators from diverse fields and schools recently received an $11.2 million grant from the National Heart, Lung and Blood Institute for a multi-pronged project aimed at reducing graft-versus-host disease — a common and potentially deadly complication of stem cell transplants used to treat blood cancers and other diseases.

Together, the work will explore the importance of the microbiome, and key metabolites produced by microbes in mitigating the severity of GVHD and improving outcomes. The effort includes both studies in mice and also a proof-of-concept clinical trial looking at the impact of dietary adjustments on patients' microbiome, metabolome and clinical outcomes.

"This project brings together a team who have worked and published together previously," says principal investigator **Pavan Reddy, M.D.**, deputy director of the Rogel Cancer Center and division chief of hematology/oncology. "These collective projects are the results of unifying our preliminary datasets over the past several years. We hope that by working collaboratively we can make a difference for patients receiving hematopoietic cell transplants."

Sarah Kearns is a freelance science writer and editor. She earned her doctorate in chemical biology from U-M in 2020.

Michigan News writer Laura Bailey also contributed to this article.

Above: James Moon, Ph.D., peers through a microscope in his lab. Below: U-M's germ-free mouse facility collaborates with investigators studying inflammation and cancer.

Illustration: Rajani Arora

Photos: Daryl Marshke/Michigan Photography; ULAM Germ-Free Mouse Facility

Found in Translation

By its nature, discovery science can be incremental and unsexy — yet it forms the backbone of innovation. Here are just a few of the insights from Rogel Cancer Center labs with the potential to transform clinical care.

By Ian Demsky | **Illustration by Jacob Dwyer**

protein involved in cholesterol metabolism plays an important — and previously unknown — role in suppressing the body's natural immune defenders in and around pancreatic tumors, a research team led by the University of Michigan Health Rogel Cancer Center reported in *Cancer Research* last year.

This discovery of a new player in the pancreatic tumor microenvironment is as typical as it is profound — one of many such nuanced insights into the biology and development of cancer being uncovered across the cancer center's labs all the time.

Here, the research team found ApoE, an apolipoprotein known to play roles in cardiovascular disease and Alzheimer's, is elevated in the blood of people with pancreatic adenocarcinoma, with higher levels of ApoE correlating with worse outcomes.

Experiments in mice that lacked the ability to produce ApoE showed reduced tumor growth and more cancer-fighting T cells around the tumors. The researchers also found that ApoE helped drive the production of two immunosuppressive proteins via the low-density lipoprotein, or LDL, receptor, a key player in cholesterol metabolism.

"Not only does our study point to blood levels of ApoE as a possible prognostic biomarker in pancreatic cancer, the findings point toward ApoE as a potential target for improving the effectiveness of chemotherapy and immunotherapy," says study first author **Samantha Kemp, Ph.D.**, who recently graduated from U-M and is now pursuing a postdoctoral fellowship at the University of Pennsylvania. "But there's still a lot we don't know. In pancreatic cancer, it remains to be determined which cell types are targets of ApoE and what functional role it plays in different types of cells."

And thus, insight by insight, our collective understanding of cancer edges forward.

Between the summer of 2020 and the summer of 2021, members of the Rogel Cancer Center contributed to some 250 papers in highly influential journals — sharing new, fundamental discoveries about cancer in places like *Nature*, *Cancer Discovery* and *Cell*.

Years of painstaking laboratory work were added to the world's pool of knowledge under dry, workaday titles like "Cancer SLC43A2 alters T cell methionine metabolism and histone methylation" and "Loss of optineurin drives cancer immune evasion via palmitoylation-dependent IFNGR1 lysosomal sorting and degradation."

"Biomedical breakthroughs most often rely on a body of discoveries that builds up over time," a recent *Nature Cancer* editorial noted. "The work that formed the basis of targeted therapies, immunotherapies and the vaccine against human papillomavirus are but a few such examples."

As one of the top institutions in the country for National Institutes of Health funding, U-M is a powerhouse of discovery science research. And the cancer center's 320-plus members are drawn from nearly 50 departments across campus — ranging from biomedical engineering to surgery, biostatistics to epidemiology, human genetics to medicinal chemistry.

"Basic science research is one of our most important missions — and our members are investigating important areas including the functions of the tumor microenvironment, key signaling changes in cancer cells and tumor stroma, and epigenetic mechanisms of cancer development," says Rogel Cancer Center Director **Eric Fearon, M.D., Ph.D.**, the Emanuel N. Maisel Professor of Oncology. "Yet it's equally important for us to continue to seek opportunities to translate this new knowledge into effective strategies for prevention, early diagnosis and treatment."

Photo: Erica Bass

Yoshie Umemura, M.D., and Daniel Wahl, M.D., Ph.D., teamed up with Wajd Al-Holou, M.D., (right) to analyze tumor tissue from glioblastoma patients.

'A sliver of hope'

Yoshie Umemura, M.D., and **Daniel Wahl, M.D., Ph.D.**, are a good example of Fearon's prescription. In 2020, they launched a clinical trial aimed at translating findings from Wahl's lab that suggested an existing immunosuppression drug may make glioblastomas more vulnerable to radiation therapy.

Despite being the most common type of malignant primary brain tumor, the five-year survival rate for glioblastoma has been stuck below 10%.

"Our main treatments are surgery, chemotherapy and radiation," says Wahl, an assistant professor of radiation oncology. "The standard chemotherapy agent, temozolomide, was approved by the FDA in 2005, when I was just starting medical school — and the needle really hasn't budged since then."

In most patients, not only do tumors come back after surgery followed by radiation, they grow in the same spot — a hallmark of the disease's inherent resistance, notes Umemura, a clinical assistant professor of neurology.

"That was the genesis of this project," Wahl says. "We wanted to understand what makes these tumors resistant to radiation — and specifically what aspects of the tumors' metabolism make them resistant."

The research team examined the characteristics of nearly two dozen glioblastoma cell lines, looking at the metabolites they produced and measuring how resistant each was to radiation.

They found that a family of metabolites called purines, which are building blocks of DNA and RNA, correlated with radiation resistance.

"GBM cells that have lots of purines are really resistant to radiation, while GBM cells that have low purines are really sensitive," Wahl says. "And once we had those data we said to ourselves, 'OK, if we intervene and take purines away from the glioblastoma cells, we might be able to make the tumors more sensitive to radiation.' "

Fortuitously, a drug that lowers purine levels had been approved by the Food and Drug Administration two decades earlier. Mycophenolate mofetil, or MMF, had proven safe and effective as an immunosuppressant to prevent organ transplant rejection. It's even available as a generic, lowering the cost of a clinical trial — and potential future treatment costs for patients.

In the lab's animal model studies, tumor growth was moderately slowed down in mice who received radiation therapy alone or MMF alone, but almost totally halted in the mice who received both. The benefits of MMF were similar whether tumors were grown in the brains of the mice or elsewhere in their bodies, demonstrating the drug's ability to effectively penetrate

Antonio Lerario, M.D., Ph.D.; M.D./Ph.D. student Dipika Mohan; and Gary Hammer, M.D., Ph.D., are turning laboratory discoveries into better treatments for adrenal cancer patients.

the blood-brain barrier — a critical factor for treating patients with brain cancer.

Repurposing a drug that had already been through the rigors of FDA approval smoothed the path between bench and bedside for Umemura and Wahl.

"If we had found a *new* metabolic enzyme that caused radiation resistance, the reality would be that we'd then have to start doing drug discovery and optimization, maybe spin out a small company, and, in 5-10 years, be ready for a clinical trial — if everything goes well," Wahl notes. "So, yes, one key part was that the drug already exists, and equally important was having a partner like Dr. Umemura who has expertise in developing clinical trials and a university that puts resources behind facilitating this type of translation."

Instead of taking years, the collaboration was able to move forward over a matter of months.

And as the trial proceeded in patients with recurrent glioblastoma, new data from U-M and elsewhere emerged indicating that MMF was indeed safe when given in conjunction with radiation as well as with chemotherapy — and that it made both chemotherapy and radiation more effective.

"That gave us the confidence to expand the trial to include patients with newly diagnosed glioblastoma as well," Umemura says. "And last August, they became eligible, too."

She adds, "The bottom line is that we really want better options for our patients. When we're in an exam room talking to a patient about their prognosis, we want to be able to give them a sliver of hope."

Bedside to bench to bedside

At the Hospital das Clínicas da Faculdade de Medicina at the University of São Paulo, **Antonio Lerario, M.D., Ph.D.**, frequently cared for patients with adrenal cancer. The disease is more common in Brazil than anywhere in the world, especially in children, due to a prevalent TP53 mutation.

Collaborations with the lab of **Gary Hammer, M.D., Ph.D.**, director of the adrenal oncology program at U-M, brought Lerario to Ann Arbor several times as a visiting researcher, and eventually led to him joining Hammer's lab as a staff scientist.

Photo: Erica Bass

"When we're in an exam room talking to a patient about their prognosis, we want to be able to give them a sliver of hope."

Yoshie Umemura, M.D.

At U-M, Lerario worked on the effort to map key genomic changes in adrenocortical carcinoma, or ACC, as part of The Cancer Genome Atlas. Michigan was instrumental in having the rare cancer included in the landmark study, and helped assemble the necessary international collaborations to reach critical mass.

"My university, the University of São Paulo, contributed samples to the study and many of them were from patients I used to see in clinic," Lerario says. "So, I knew very intimately the details and history of these patients. That was a motivation for me to come and study these patients' clinical manifestations at a molecular level."

The TCGA project, which was published in 2016, identified three distinct molecular subtypes of adrenal cancer — laying the foundation for the group's continuing efforts to turn those insights into new tests and desperately needed treatments.

"Up to 75% of all patients will eventually develop metastatic disease, and our current medical therapies for ACC provide limited — if any — survival benefit," Lerario, Hammer and their co-authors noted in a 2019 commentary.

"While [tumor] grade is certainly effective in pinpointing patients who are less likely to respond to standard of care, such an approach still falls short of rationally directing patients to therapy based on oncogenic pathways driving their specific type of ACC," they wrote.

Building on TCGA insights, Lerario and **Dipika Mohan**, an M.D./Ph.D. student in Hammer's lab, led the development of an inexpensive, rapid PCR test that boils down a knotty genome-wide signature to a single, yes/no biomarker that can identify whether a patient has the most aggressive of the three flavors of adrenal cancer — with strong potential to guide clinical decision making. (The university has filed for patent protection on the technique.)

More aggressive treatment may be warranted for patients who have the marker because they are unlikely to be helped by mitotane, which is often prescribed after surgery to kill lingering adrenal cancer cells and prevent recurrence, according to retrospective findings the group presented at the 8th International Adrenal Cancer Symposium last fall.

"Of course, guideline-based therapy is best," Mohan says. "But because it's such a rare cancer, doctors also rely a lot on institutional expertise. These tumors have very high proliferation rates, and we're working with collaborators in Brazil who are using our biomarker assay to try to identify patients who might benefit from earlier cytotoxic chemotherapy — which kills rapidly dividing cells — to shrink the tumors before surgery to help treatment be more effective."

The team is also exploring whether a blood test to capture circulating tumor DNA could be used to classify a patient's adrenal cancer subtype earlier and non-invasively.

Future tech

Sometimes, innovation means tapping into emerging technologies to improve patient care. Building on their previous research in animal models, **Muneesh Tewari, M.D., Ph.D.**, and **Sung Won Choi, M.D.**, recently teamed up on a small trial that used commercially available, wearable thermometers to detect dangerous complications in hospitalized cancer patients hours earlier than routine monitoring.

The device, which takes readings every two minutes and wirelessly transmits them to the cloud, was able to quickly detect adverse events that affect body temperature, like infection and cytokine release syndrome, in patients who received a hematopoietic stem cell transplant or CAR T-cell therapy — thus allowing for swifter interventions, according to findings their team published in *Cancer Cell*.

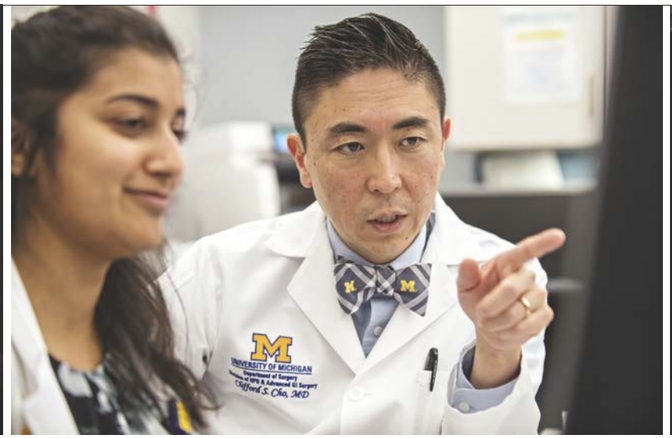
The study also examined more subtle changes in temperature that may appear as deviations from the patient's baseline circadian pattern, signaling a potential problem before a steep temperature rise.

"This additional lead time is clinically significant for patients with cancer, who are commonly immunocompromised and at risk for infection," says Tewari, a professor of internal medicine and of biomedical engineering. "How quickly doctors can administer antibiotics can play an important role in combatting potentially fatal infections and sepsis."

The monitoring approach could also facilitate moving some costly inpatient CAR-T care to the outpatient setting by providing additional lead time for the patient to return if a problem was detected, adds Choi, the Edith S. Briskin and Shirley K. Schlafer Foundation Research Professor of Pediatrics. (The study authors and university are pursuing intellectual property protections on the work.)

Meanwhile, other cancer center members are pioneering entirely new technologies.

Zhen Xu, Ph.D., a professor of biomedical engineering, and a team of U-M of colleagues developed histotripsy, a non-invasive ultrasonic surgical approach. After nearly 20 years of development, a clinical trial



Left to Right: Innovators Zhen Xu, Ph.D.; Clifford Cho, M.D.; and Arul Chinnaiyan, M.D., Ph.D. and Yashar Niknafs, Ph.D.

deploying histotripsy against liver cancer recently launched at U-M and seven other sites across the U.S. The trial, which is also being conducted in Europe, is sponsored by HistoSonics, a U-M start-up commercializing the group's research. (The inventors and university have a financial stake in the company's success.)

Of course, using ultrasonic pulses is nothing new to medicine, but the process behind histotripsy is. While previous techniques used ultrasound to generate heat energy to ablate tissues, histotripsy harnesses the ultrasound energy to activate thousands of microbubbles at the target — called cavitation — to emulsify tissue. And it can do so with great precision, narrowly targeting the tissues of interest with millimeter accuracy.

"When we started, cavitation was seen as a process to be avoided at all costs," Xu says. "These microbubbles are on the size-order of cells. So, our idea was to use ultrasound to harness and focus this gas we naturally have in our bodies and use these 'micro-scalpels' to target tissue."

The technology is potentially revolutionary on several fronts. It uses an external beam, similar to radiation therapy, which means you don't have to cut into a patient. But more than that, doctors have the advantage of being able to guide the beam using real-time visualization of the target.

"It's non-ionizing, non-toxic and non-thermal," she says. "Huge advantages."

Results from a small, phase 1 trial in liver cancer at three sites in Spain were reported at the February 2020 Society of Interventional Oncology annual meeting. Histotripsy was found to be safe and well-tolerated, and researchers reported the targeted tumors had contracted by 36% after a week, 54% after a month, and 72% after two months.

Additionally, echoing findings from animal studies, in two of the eight patients, tumors other than the ones that were directly targeted also shrank or stabilized following treatment.

This is believed to be a result of a larger immune response triggered by the procedure. Earlier that year, a team led by Xu and co-senior study author **Clifford Cho, M.D.**, a professor of surgery, reported histotripsy ablation stimulated a profound immune response in mouse models of melanoma and liver cancer — and this stimulation of tumor-specific immune response was capable of magnifying the impact of checkpoint inhibition immunotherapy.

"This is a very interesting and exciting discovery for the future of histotripsy research," Xu says. "In rodent models, we did several experiments that showed if you treat a portion of the tumor, the remaining tumor can also shrink and disappear, or if you treat one tumor, a distant tumor may also shrink — because the immune system is stimulated to go after more of the cancer."

In June 2021, U-M joined sites around the country in enrolling patients in the #HOPE4LIVER trial, the first large-scale study to evaluate the use of histotripsy against cancer, testing the technology in patients with primary and metastatic liver tumors.

"This research started here, and we are very excited to help move this technology out of the laboratory and into a clinical trial where we can evaluate its safety and efficacy for patients," says interventional radiologist **Mishal Mendiratta-Lala, M.D.**, the principal investigator of the U-M trial site.

Unexpected connections

It's often unclear when and how discovery science research might pay off. Serendipity often plays a role both in developing new insights and in applying them outside the lab.

Foundational work at U-M uncovered an important gene fusion on-switch for prostate cancer development that has led to the development of a new, sensitive, urine-based prostate cancer test. It also points to new potential prevention and treatment possibilities against COVID-19.

"We weren't exploring this area, but we knew that coronaviruses use two key host proteins to gain entry and replicate within cells," says **Arul Chinnaiyan, M.D., Ph.D.**, director of the Michigan Center for Translational Pathology. "One of those proteins is TMPRSS2. This was appealing because we had discovered TMPRSS2-ETS gene fusions in prostate cancer and knew that TMPRSS2 was regulated by the androgen receptor. It made a lot of sense to explore this in the context of SARS-CoV-2."

Chinnaiyan received a $390,000 grant from the National Cancer Institute to explore the possible role of TMPRSS2 in SARS-CoV-2, and whether treatments commonly used in prostate cancer could potentially be rallied to fight COVID-19.

"The studies we have conducted provide a strong rationale for the use of androgen receptor or BET inhibitors in COVID-19 treatment to decrease TMPRSS2 expression, and that of another key protein, ACE2," he says.

The original TMPRSS2 findings, which were published in *Science* in 2005, have also led to the development of a urine-based test called MyProstateScore, which is being commercialized by LynxDX, a U-M start-up company. (The inventors and university have a financial stake in the test's success.)

"The test gives us a non-invasive way to look at a set of exclusive and specific biomarkers to predict whether a patient has an aggressive form of prostate cancer before we move on to an MRI or a biopsy, rather than having everyone with a high prostate-specific antigen level automatically undergo a biopsy," says Chinnaiyan, a co-founder of LynxDx.

A retrospective validation study published in *The Journal of Urology* found that the MyProstateScore test could have avoided nearly 400 unnecessary biopsies in a cohort of 1,500 patients while failing to flag only 10 aggressive cancers. The test is already available to patients at U-M and the surrounding area.

"There's been a lot of serendipity since the beginning," says Chinnaiyan, the S.P. Hicks Endowed Professor of Pathology and a Howard Hughes Medical Institute investigator.

The initial discovery that the gene fusion underlay 50-60% of all prostate cancers was unexpected, he notes. Gene fusions and translocations were known to be the molecular basis for blood and soft tissue cancers, but virtually unknown in solid tumors at the time.

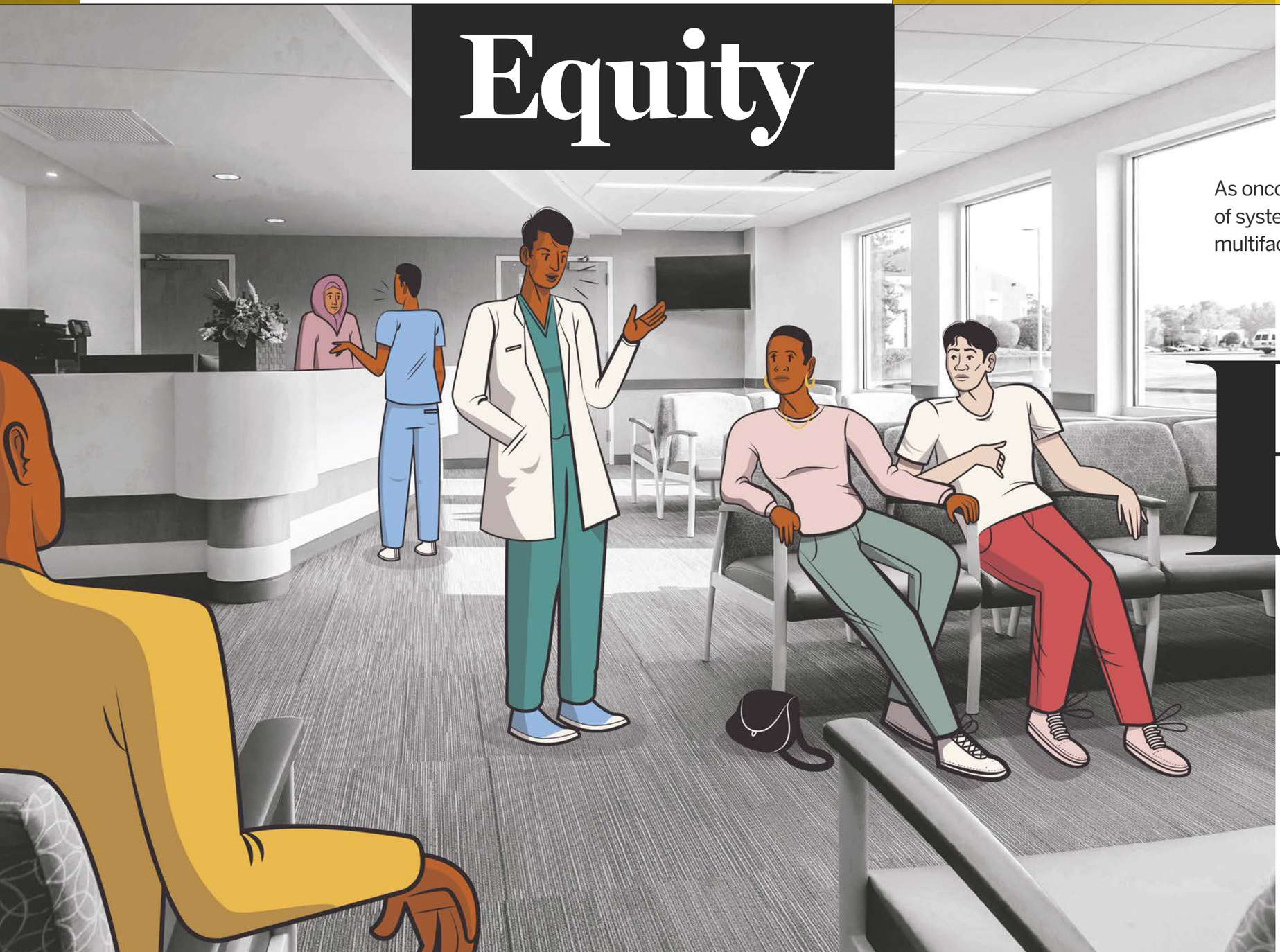
"It was actually a bit shocking," he notes.

And, of course, back in the early 2000s, there was no way Chinnaiyan and his collaborators could have anticipated that their discovery might have implications in a future pandemic featuring a novel coronavirus that attacks the lungs.

"Still, it's a homerun hypothesis to pursue," he says. "We have most of the samples we need for this study already banked in our lab. We just never really looked at the lung because there was no reason to at the time. Now we are going back and doing that analysis."

Photos: Courtesy of Michigan Medicine Office of Development (Xu); Leisa Thompson

Emphasizing Equity



As oncology grapples with the country's legacy of systemic racism, the Rogel Cancer Center is leading multifaceted efforts to improve health outcomes.

By Mary Clare Fischer

Illustrations by Justine Ross

Every corner of Michigan Medicine clamors for **Erika Newman**'s expertise.

As an associate professor, interim head of pediatric surgery, cancer scientist and diversity leader, her calendar is filled to the margins with meetings, research, surgeries and interviews.

So, when the University of Michigan Health Rogel Cancer Center was looking to fill a new position for associate director of diversity, equity, inclusion and justice, the cancer center's chief administrator, Julie Brabbs, was hesitant to ask Newman if she was interested.

But when Brabbs did, Newman knew she couldn't say no — not just because she was eminently qualified, having spearheaded diversity efforts for both the Department of Surgery and more broadly as the associate chief clinical officer for health equity for the U-M Medical Group. And not just because as a person of color, she and her family experience disparities every day. ("We were born into this," she says. "It's not like you have a choice.")

Mostly, Newman couldn't turn down this opportunity because her mother needed more time.

Newman's mother was diagnosed with metastatic cancer as Newman was starting medical school. The two were best friends, she says, particularly close because Newman is an only child whose father was killed when she was 3 years old.

Yet their bond couldn't save her mother, who died at age 45.

"What has been most painful to me is that I know she didn't have access to a cancer center like Rogel," Newman says. "She was being cared for in our local community hospital that was doing the best they could with limited resources. It was nothing like how patients are cared for here. And I wish my mom would have had an opportunity to come to a place like Rogel. It's something I think about every single day."

"So, if I have an opportunity for us to improve access for patients that may not have an opportunity to get excellent care here," Newman says, "then I'm going to do that."

She's not the only Rogel Cancer Center leader who feels this way. Combating cancer disparities has been a longtime priority for Michigan's highest ranked cancer center, well before events like the Black Lives Matter movement and the COVID-19 pandemic broadened the public consciousness of society's systemic inequities.

"The entire leadership team is deeply involved and committed to intervening and reducing these disparities," says **Ken Resnicow, Ph.D.**, Rogel's associate director for community outreach, engagement and health disparities, whose job description has included disparity research since he was first hired in 2003. "And we try to promote it in every nook and cranny of the cancer center so people are aware, particularly of the key disparities across the state. Of course, we care about national numbers, but the emphasis is on taking care of our local communities."

Starting in 2017, the National Cancer Institute required NCI-designated cancer centers, including Rogel, to put additional resources toward the topic of disparities, with the promise of additional funding to support them. As a result, the cancer center has spent the past few years making even greater investments in everything from basic science research and health communications projects to community outreach and recruitment, all in the name of increasing equity in cancer care.

Although Newman was still outlining her long-term goals for her position at the time of the interview, she says the cancer center's comprehensive approach already lines up with the framework she uses to describe how she thinks about leadership.

"I have these L words I use," she says. "You start the journey by learning more."

'Learning more'

"Hello everyone, my name is Bob Dess," echoes a recorded voice. "I'm a radiation oncologist here at the University of Michigan, and it's my pleasure to speak to ASCO today on 'Prostate Cancer: Rejecting the biologic basis for outcomes disparities.'"

Robert Dess, M.D., is presenting at the American Society of Clinical Oncology's annual meeting, the world's largest cancer conference. A few years ago, he was the first author on one of the biggest studies to date to analyze outcomes associated with prostate cancer — a cancer that serves as a quintessential example of inequality.

From 2014 to 2018, Black people in the state of Michigan were 1.6 times as likely to be diagnosed with prostate cancer as whites and twice as likely to die from it, with similar numbers seen nationwide. Those who are Black also have higher rates of metastatic prostate cancer, and the odds are greater that they experience complications from treatment.

"Equity work is not a one-and-done thing."

Lori J. Pierce, M.D.

For a long time, the prevailing theory in the scientific community was that genetic differences were the source of different racial groups' propensity, or lack thereof, to not only develop chronic diseases like cancer but also to experience worse outcomes. Yet, as race has been increasingly recognized as a social construct, Rogel Cancer Center researchers like Dess are exploring the source of illness through a clearer lens — one that considers the many societal, economic and environmental factors that play into whether a tumor grows and spreads within a human body.

For example, Dess and his team demonstrated that when Black and white patients with prostate cancer were given equal access to treatment, the disparities vanished — supporting the idea that the amount of melanin in your skin isn't as relevant as the care you receive.

Elena Stoffel, M.D., M.P.H., a clinical associate professor of internal medicine/gastroenterology, and **Laura Rozek, Ph.D.**, an associate professor of environmental health sciences, nutritional sciences and global public health, are interested in the origins of the problem: namely, how biological and environmental factors impact an individual's risk for developing colorectal cancer.

About 1 in 10 colorectal cancers are diagnosed before age 50, and colorectal cancer cases have continued to increase. Incidence of colorectal cancer is higher among Black people compared to white people, with Black people more likely to develop cancer at younger ages.

The pair is taking a multifaceted approach to examining racial disparities in colorectal cancer, teaming up with the Barbara Ann Karmanos Cancer Institute and Louisiana State University to recruit patients of different ethnicities diagnosed with colorectal cancer, and comparing the molecular makeup of tumors from patients who live in Michigan versus Louisiana.

"What we're recognizing is that not all colon cancers are the same and that identifying particular characteristics about each tumor may give us a better sense of how it developed and how best to treat it," Stoffel says. "And we're exploring whether there's something about potential differences in the way we live or differences in environmental factors, stress, or health behaviors that may impact the likelihood of developing a tumor and/or influence tumor behavior."

The hypothesis arrived at by **John M. Carethers, M.D.**, is that inflammation in the gut microbiome triggered by certain diets is partially to blame for the racial disparity. Carethers, who chairs the Department of Internal Medicine, has for decades been studying how the breakdown of DNA repair mechanisms contributes to the development of cancer, and he recently received a grant from the National Institutes of Health to further explore one that seems to be affected by inflammation — and that is more common in Black people.

"We always say the high-fiber, low-fat diet or the Med-

John M. Carethers, M.D.

'Language Matters'

Debbie Chen, M.D.

LANGUAGE IS ANOTHER area where Rogel researchers are working to lower barriers and improve outcomes. English is the primary language of **Debbie Chen, M.D.** But it's not her parents' or several of her aunts' and uncles', who mostly speak Cantonese.

They're part of the 20 percent of Americans — 60 million people — who speak a language other than English at home. Yet, as Chen, a clinical lecturer in endocrinology, discovered, individuals with limited English proficiency and the barriers they face in cancer care are understudied.

Chen is changing that. Thanks to a recent grant from the cancer center, she's exploring disparities in access to cancer care for Chinese and Spanish speakers with thyroid, lung or colon cancer. Her long-term goal: Using the data to inform real-world improvements for this population's care.

"Having the opportunity to do this research is exciting because it's not only adding to our understanding about cancer disparities," Chen says, "but we're also highlighting some different needs within our health care system — and it would be transformative if we could get the people designing and thinking about cancer care to keep these issues in mind."

“So, if I have an opportunity for us to improve access for patients that may not have an opportunity to get excellent care here, then I’m going to do that.”

Erika Newman, M.D.

iterranean diet is a good diet to lower the risk of colon cancer,” Carethers says. “But whether you have access to that or not comes down to socioeconomics: Where do you live? What kind of grocery stores are near you? Are you in a grocery store desert — and if so, and that’s the type of diet you have for 50, 60, 70 years, what kind of food products are you feeding into the microbiome?

“That could explain some of the disparity,” he continues. “If you have the right inflammatory milieu mixed with the right genetic background, maybe that’s why you’re getting cancer.”

When the grant is complete, he’ll have more answers. But, for Carethers and many researchers at the cancer center, such study results represent not the end of a search, but really a new beginning.

“The challenge is always to figure out the primary drivers of the disparities,” Dess says, “because if you understand primary drivers, then you can start thinking about solutions.”

‘Listening more’

Between May and September 2019, the shoppers at several Dearborn grocery stores encountered an unfamiliar sight: folding tables stocked with tablets, paper questionnaires and $25 gift cards. Each table was staffed by a representative from the Arab Community Center for Economic and Social Services, better known as ACCESS, a community-based health and mental health center for Arab Americans.

The Rogel Cancer Center had partnered with ACCESS to survey those who identify as Middle Eastern or North African (MENA) about their knowledge, attitudes, beliefs, barriers and behaviors. Since Southeast Michigan boasts one of the largest MENA populations in the United States, the cancer center sees many MENA people for treatment and has identified the community as a priority group to improve health.

But outreach and engagement is most successful when the person reaching out has a strong relationship with the person engaging. In many instances, the cancer center’s community outreach and engagement team already has those connections. But ACCESS has spent half a century establishing trust with this particular community and knew what was necessary to make an impact with the MENA people: meeting them where they were.

So, backed by cancer center funds, ACCESS staffers and volunteers took to Arab-owned grocery stores, and colleges, and mosques. Their surveys asked questions about cancer screening — Where were people seeking cancer care? What were their perceptions of the different options available to them? — as well as about financial stress, barriers to care, discrimination, immigration status, and culturally specific risk factors

Photo: Scott C. Soderberg/Michigan Photography

like hookah smoking. Ultimately, they received responses from more than 400 people.

“We were able to identify a variety of barriers to optimal health for this population,” says **Minal Patel, Ph.D., M.P.H.**, an associate professor of health behavior and health education. “These raised questions around modesty issues and culture and religion that could lend to thinking about innovative ways of delivering culturally appropriate care.”

Since then, studies led by **Diane Harper, M.D., M.P.H.**, a professor of family medicine and of obstetrics and gynecology, examining at-home HPV screenings have intentionally included MENA individuals. (HPV testing is an effective method for cervical cancer screening partly because such a large proportion of cervical cancers are caused by the human papillomavirus.)

Preliminary data has shown that these DIY tests are more convenient and comfortable for the majority of participants, with multiple MENA women commenting that the tests were less embarrassing and preferred to a physician exam.

The disparities interventions haven’t stopped there. Resnicow has created a culturally tailored texting program in both English and Arabic to try to get tobacco use, both cigarettes and hookah, down in the MENA community. And Patel and **Jennifer Griggs, M.D., M.P.H.**, a professor of hematology/oncology, are looking at ways to improve the financial burdens for cancer patients on a large scale.

Meanwhile, in partnership with the Michigan Oncology Quality Consortium, Resnicow, Griggs and Stoffel are seeking to improve care for Michiganders

Ken Resnicow, Ph.D. uses motivational interviewing techniques to help craft tailored interventions.

who have a genetic predisposition to cancer.

Their clinical trial, funded by the National Cancer Institute's Beau Biden Cancer Moonshot initiative, helps identify cancer patients who meet the criteria to be genetically tested for hereditary cancer syndromes. Hereditary cancer syndromes are more common than previously thought and are associated with risks for many different types of cancer — yet the vast majority of patients who seek genetics services are white women worried about their risk for breast cancer.

Griggs started working with the design team that developed the family health history tool for the study more than a year ago to make it more inclusive or, as Erika Newman, who was recently named the Michael W. Mulholland, M.D., Ph.D. Research Professor, puts it, to "lower bias."

The first question it previously asked was whether patients knew their family members' health histories or whether they were adopted. Those were the only two choices.

"There are a lot of families that don't have a mom, a dad and two kids," Griggs says. "There are surrogacies, and there are people who are estranged from their family of origin, and people who may not be in touch with one or another parent due to a multitude of reasons. So, we started looking at different options."

Other problems remained: If you are a woman, the only cancers you could pick from in your family history were associated with traditionally female reproductive organs. On the flip side, if you said that your brother had cancer, the choices didn't include ovarian or endometrial cancer. Now that the researchers have revised the form, participants can note that family members of any gender have had any cancer.

"The goal was to reduce systematic harms done to non-binary and trans people as well as intersex people through questionnaires and surveys," Griggs says.

People who participate in the statewide project will be asked about their family history of cancer as well as their values, motivations and any concerns they might have about genetic testing. Based on their responses, patients who are eligible for genetic testing will receive tailored messages providing information about how to access genetic testing services and how the results could inform their care.

"We're finding out how we can decrease the barriers that we've put into place," says Griggs, who is also a professor of health management and policy. "It's not as if our patients don't know about the cancer in their family. Rather, we've failed to meet their needs. So now we're doing this through an equity lens and a 'closing the gap' lens that requires going to communities and creating trusting relationships."

'Leading with love and compassion'

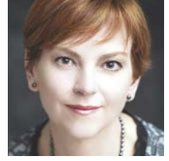
When it was time for **Lori Pierce, M.D.**, to cap off an extraordinary year as the first African American female president of ASCO, she knew where she wanted to give her final remarks.

Pierce, a professor of radiation oncology and vice provost of academic and faculty affairs across U-M, chose the Michigan League, a building that has sat at the north end of U-M's central campus for almost 100 years. Its brick-and-stone facade, punctuated with stained glass windows, gives the appearance of an art deco-era high school mixed with a grand church — a gathering place for both education and community.

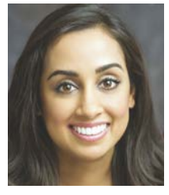
"The League was created in 1929 for women and by women as a place where they could congregate," Pierce intoned, flanked by the building's ornate paneling, during ASCO's annual meeting. "And that was necessary because, up until 1956, women were not allowed in the main student union. It was exclusive to men unless women were escorted by a man, and then they had to use the side door.

"So, I thought the League would be a perfect location for me to open our annual meeting," Pierce added, "and to deliver my presidential address, which will focus on equity."

Pierce has become a standard-bearer for the issue as it relates to cancer care and research. As ASCO president, she didn't simply describe the underrepresentation in health care that she'd personally witnessed visiting family in segregated North Carolina as a child. She invented and invested in solutions — like a fund for further research on disparities in cancer care, a podcast to educate providers about the impact of the social determinants of health and a collaboration with the Association of Community Cancer Centers to test strategies around increasing Black and Latinx participation in clinical trials.



Jennifer Griggs, M.D., M.P.H.



Minal Patel, Ph.D., M.P.H.

Lori Pierce, M.D.

It was ideal timing, as the national attention to endemic injustices grew and grew.

"It's having a cell phone to be able to videotape things in real time," she says. "Acts that have been going on for hundreds of years can now be brought to your television on the national news at 6 o'clock in the evening. It has evoked a feeling in the country and throughout the world that the status quo is not acceptable, and change has to come and has to come now."

And, at Rogel, change *is* coming now. It's in the tweaks to forms that Jennifer Griggs has made to help people who have already been marginalized for so long feel recognized and accepted. It's in the questions Ken Resnicow asks different cultural groups to encourage adoption of healthier behaviors. It's in the grants that Debbie Chen has received to improve the health care experience for Americans who primarily speak a language other than English. And it is in Erika Newman's efforts to create a deep sense of belonging and anti-racism throughout the organization and the communities it is trying to better serve.

What is most important, though, is that the change continues.

"Equity work is not a one-and-done thing," Pierce says. "It's a constant, constant commitment. And that consistency in terms of commitment is what the community starts to see."

'Leveling the Pipeline'

Jamie Mitchell, Ph.D., M.S.W.

CLINICAL TRIALS ARE most effective when their samples represent patients who are diagnosed with cancer the most, but often they don't. About 5% of clinical trial participants nationwide are Black, despite the higher incidence of most cancers in people of color.

"We need to know that those who are most affected by a disease are included in the testing of interventions," says **Jamie Mitchell, Ph.D., M.S.W.**, the assistant director of clinical research participation at the cancer center, who's working on a plethora of ways to diversify clinical trial recruitment.

Photo: Daryl Marshke/Michigan Photography

‘We might for the first time really be thinking of cures of cancer’

Interview by Nicole Fawcett

When **Max Wicha, M.D.**, was starting his career, oncology did not come highly recommended.

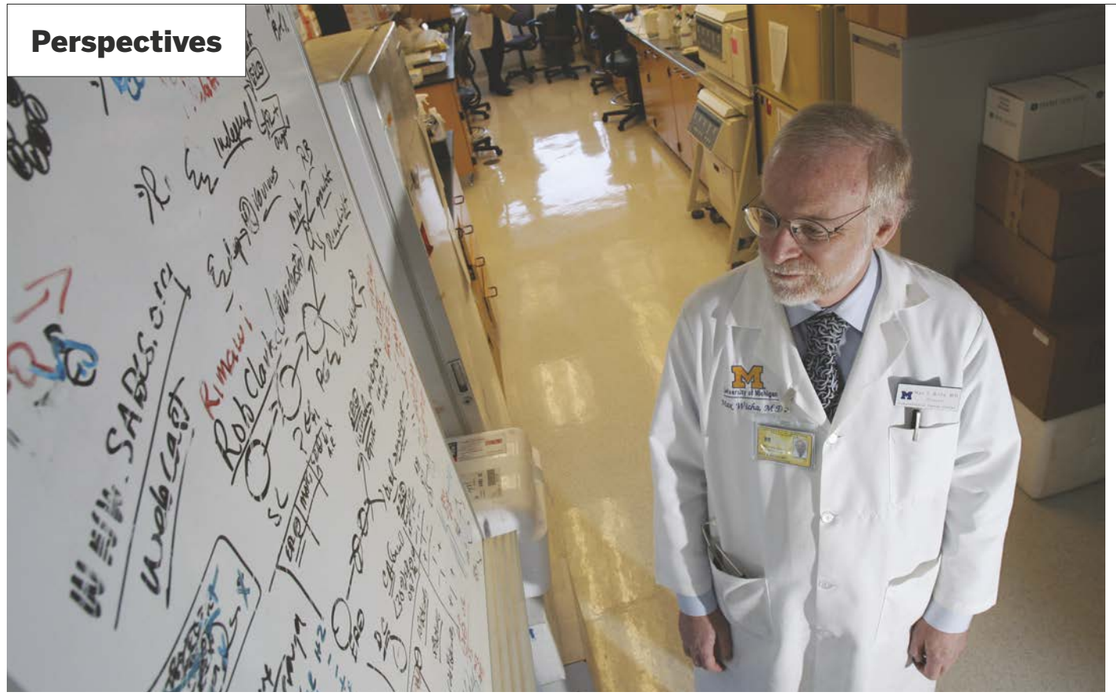
“When I first got into this field about 40 years ago, I went for advice to someone who was very senior in medicine. I said I want to go into cancer research and become an oncologist. They looked at me and said, ‘Why would you want to waste your life on that? We’re not going to make progress against cancer. It’s the least scientific of any discipline. Go into some other field where you can really use science,’” Wicha recalled.

“Of course, that turned out to be completely wrong.”

In fact, Wicha, the Madeline and Sidney Forbes Professor of Oncology and founding director of the Rogel Cancer Center, jumped into the discipline just as it was taking off.

On the heels of the National Cancer Act’s 50th anniversary, Wicha reflects on the evolution of the field. ➔

Photo: Leisa Thompson



This 2007 *New York Times* photo of Max Wicha, M.D., in his lab accompanied a story on stem cells' role in cancer.

When you were getting started, were you surprised by your mentor's criticism of the field?

What they said in a sense was true. Forty years ago, there was a tremendous disconnect between research to understand the biology of cancer and the clinical practice of oncology. The clinical care had very little to do with the science that was brewing in the laboratory.

Initially, when chemotherapy was developed, medical oncologists thought if we find the right combination of chemotherapy, we can cure most patients with cancer. That turned out to be naïve, and there was a lot of discouragement among clinicians when their clinical trials didn't improve outcomes.

At the same time, basic scientists were coming up with dramatic results in the laboratory, with the first discoveries of oncogenes and tumor suppressor genes.

The basic scientists were saying, 'Look, we're starting to understand what cancer is.' But if you went to the clinic, you didn't see any impact. That was the dichotomy of the field.

How did the National Cancer Act and the beginning of cancer centers start to change this?

To make a fundamental impact, we knew we had to take the basic research and figure out how it leads to improvements for patients — not just make discoveries in the laboratory.

Cancer centers became a lot of the engine for cancer research and cancer discovery, which propelled us into the dramatic impact we see now. It's because of this marriage of basic research, clinical research and what we now call translational research.

When you were tasked with creating a cancer center at the University of Michigan, how did this landscape influence your approach?

The challenge was how to get these groups to merge and talk to each other. On the clinical side, we had people in each discipline treating patients in different ways. Not only did they not talk to the basic laboratory scientists, but even more challenging, they didn't talk to each other.

In my own field of breast cancer, a woman then would have to visit multiple specialists, sometimes getting contradictory opinions. It could take more than a month. Patients would say, 'Why don't you put your heads together.' Of course, that was the right advice.

When we started organizing our cancer center, we decided to experiment with a multidisciplinary breast clinic. We organized either the first or second multidisciplinary clinic in the country. It was a success right from the beginning. Now of course everyone does it.

Then when we started organizing a cancer center, I thought the way to do this was around multidisciplinary programs for each type of cancer. It allowed us for the first time to bring together active teams of people from different disciplines who work on a particular cancer. It enabled us to start introducing basic scientists to clinicians and move to a more scientific approach to treat patients.

Where are we now in the progress against cancer?

It's completely flipped around. Right now, cancer is the most scientific discipline. It's the best example of basic research discoveries changing clinical care.

Melanoma is a good example. First, we developed molecular targeted therapies based on specific mutations in the tumor. But even more successful has been the use of immune stimulators. Here's a disease that was completely fatal. Now, about 60% of patients see a very significant benefit from immunotherapy. Even more exciting, for a percentage of patients, the melanoma isn't coming back. We might for the first time really be thinking of cures of cancer.

In my field of breast cancer, we've developed so many different treatments that often we can turn metastatic cancers into chronic diseases. I have patients who have had metastatic breast cancer for over 20 years.

The trick now is to understand what's different about the exceptional responders and get more patients into that realm. And the real challenge is going to be how to apply this to tumors where we haven't made much progress, like pancreas cancer and brain tumors.

I will almost guarantee you that progress in those areas won't be by accident but by studying the basic biology of those cancers and then applying new ideas based on that.

Are you glad you decided to go into oncology after all?

Personally, it's been such a privilege, and I've been so fortunate to have been in oncology during this phase when it went from a primitive discipline to being a scientific discipline making huge advances.

4 Biggest Cancer Research Breakthroughs

Major recent breakthroughs in cancer research are leading to cures and turning metastatic cancer into more of a chronic, managed disease. These are four areas of research **Max Wicha, M.D.**, says are having the biggest impact:

Immunotherapy
Wicha called this "the biggest breakthrough in cancer research over the last decade." Ongoing work will uncover how to make immunotherapy effective for more patients.

Targeted therapies
These treatments have led to huge progress in breast cancer, melanoma, lung cancer and others by targeting specific genetic alterations within tumors.

Epigenetics
Tumors can change from one type of cell to another, leading researchers to explore the idea of manipulating the epigenome to find new ways to attack cancer.

Cancer metabolism
Different cancers have common metabolic endpoints. Can targeting these commonalities make it harder for the tumor to develop resistance, since all the mutations funnel downstream to them?

The National Cancer Institute awarded U-M its cancer center designation in 1998. Max Wicha (center) served as founding director, Marcy Waldinger as administrator and Alfred Chang, M.D., as deputy director.

Photo: Fabrizio Costantini /The New York Times/Redux

Photo: U-M File

Bringing Harmony to Advanced Breast Cancer Care

Aki Morikawa and her team are ensuring breast cancer patients with CNS metastases receive coordinated care

Aki Morikawa, M.D., Ph.D., helps coordinate specialty care for patients with advanced brain cancer — similar to the way musicians cooperate when playing together.

By Staci Vernick

In a classical chamber music piano quartet, each musician raises the individual voices of piano, violin, viola, and cello in concert to bring a musical composition to life.

Much like a chamber quartet, a team of specialists at the Rogel Cancer Center bring their individual expertise to the coordinated, multidisciplinary care of patients with metastatic breast cancer through a new program called IMPACT the Brain. With a master's degree in piano performance and a seat in a U-M chamber music quintet, IMPACT team leader **Aki Morikawa, M.D., Ph.D.**, understands the value of every voice playing in tune, striking the right chords at the right moment.

"Each player has their own special expertise, but we all have to work together to come up with a coordinated care plan for our patients," Morikawa says.

Rogel's IMPACT program — for Improve Metastatic Breast Cancer Patient Access to Coordinated Treatment — is a collaboration of medical, surgical and radiation oncologists, and specialists in genetic testing and counseling, physical rehabilitation, neuropsychology and palliative care. It is single point of care coordination for patients with advanced disease.

The central nervous system is not the most common site for breast cancer metastases, but CNS metastases — which include spread to the brain — are uniquely difficult to treat and typically have worse outcomes. These particularities require a multi-specialty approach, Morikawa says.

For example, while drug therapies may be medical oncologists' preferred approach to treat breast cancer, the blood-brain barrier can reduce their effectiveness. Surgery and radiation therapy then become options for these patients.

Also, CNS metastases severely impact patients' physical function and quality of life. Brain metastases may cause double vision or seizures, so patients can't drive a car anymore, or have trouble with daily activities, says Morikawa, an assistant clinical professor and medical oncologist. Many patients become too weak to walk, and they may have issues with incontinence. Neuro-oncologists, and physical rehabilitation and neurocognitive specialists are needed to round out the care team.

The challenge lies in coordinating all of those players and addressing any gaps in care.

From a referring physician's standpoint, it can be difficult and time-consuming to navigate the system and make referrals to all the needed specialists. To a cancer patient or caregiver, it can simply be an overwhelming barrier to care.

This was the impetus for IMPACT.

With funding from the National Comprehensive Cancer Center Network Oncology Research Program and Pfizer, Morikawa and colleagues launched a small quality improvement study in May 2020 to try to improve access to coordinated care for breast cancer patients with CNS metastases. A dedicated program coordinator provided patient navigation, education, referrals to seven sub-specialties, and clinical trial screening for a cohort of 40 patients. Investigators tracked referrals and patient-reported outcomes.

In an abstract published in August in *Neuro-Oncology Advances*, the researchers report that IMPACT allows for better patient access to care across sub-specialties. The vast majority of patient feedback surveys reflected the high value placed on personalized care coordination.

Importantly, Morikawa says, they found IMPACT supports participation in clinical research for a group of cancer patients who are historically underrepresented in research studies because of their brain metastases. Among enrolled patients, 17 participated in metastatic breast cancer clinical trials.

Rogel is one of the few cancer centers that offer clinical trials for CNS metastases, with nine Phase 1, 2 and 3 studies underway for molecular targeted therapies, and radiotheranostics (radiation therapies and diagnostics). Morikawa is the lead investigator on three studies of targeted drug therapies.

"We're fortunate at Rogel to have access to all of these specialists who are wonderful collaborators and share their expertise."

Aki Morikawa, M.D., Ph.D.

IMPACT is among only a handful of similar programs in the country, all located at major academic medical centers like Michigan Medicine.

"We're fortunate at Rogel to have access to all of these specialists who are wonderful collaborators and share their expertise," Morikawa says. "Many community hospitals and smaller practices typically do not."

Metastatic breast cancer research might at first seem like an odd career path for a young woman who fell in love with the piano. After earning her bachelor's and master's degrees in piano performance at Boston University School of Arts, she appeared destined to become a professional musician.

But as it turns out, cancer research is literally in her genes. Both of her parents were cancer researchers, and she lost her father and an uncle to the disease. And while her family praised her musical talent and ambition, the practical work ethic instilled through her Japanese upbringing won the day. "My parents, you know, wanted me to have what they considered a *real* job," she says, laughing.

Morikawa went on to earn an M.P.H. in epidemiology and biostatistics at Boston University School of Public Health, and a Ph.D. in epidemiology and M.D. from Emory University. She completed an internal medicine residency at Emory, then a medical oncology fellowship at Memorial Sloan Kettering. It was there that she met her husband, Patrick Burke, M.D., a clinical assistant professor and leukemia specialist. The pair of clinician-researchers joined Rogel in 2014.

She continues with her music, she says, because it's a good therapeutic outlet for balancing her cancer research and caring for patients. Morikawa plays piano for a chamber quintet with members of Michigan Medicine's Life Sciences Orchestra.

What's on Morikawa's horizon?

"IMPACT is preliminary data showing us the needs and challenges of care coordination in this patient population. We want to build on this quality improvement. Can we apply it to other tumor types, for example?" she asks.

Ultimately, Morikawa sees this fruitful multidisciplinary collaboration in translational research leading to more clinical trials of genomically-guided approaches, and new options for patients with advanced metastatic disease. ⊠

Photo: Leisa Thompson

Feedback Loops

Postdoctoral fellow Zeribe Nwosu has challenged himself at every step of his journey to the forefront of cancer metabolism research

By Nicole Fawcett

Zeribe Nwosu, Ph.D., ended up at Michigan after a Rogel researcher challenged his poster at a conference.

At each fork in the road, **Zeribe Nwosu, Ph.D.**, has been unafraid to change course. His studies have taken him from Nigeria to England, Germany and now Michigan. Over the course of this trajectory, he also adjusted his research focus from cardiovascular disease to various cancer types, notably liver and pancreatic cancer.

His choices have been based on a clear view of his driving purpose and a willingness to step out of his comfort zone in pursuit of that vision.

"At the center of it all, I want to do something that will help patients. That is why I had no difficulty accepting a switch to working on cancer. When I reflected on it, cancer was just as big a problem as heart disease," Nwosu says.

Today, as a postdoctoral trainee in the labs of **Costas Lyssiotis, Ph.D.**, and **Marina Pasca Di Magliano, Ph.D.**, Nwosu is focused on the intersection of metabolism, genomics and the immune system in pancreatic cancer — asking questions like: How do pancreatic cancer cells feed? How do immune cells impact pancreatic cancer metabolism? What gene signatures control tumor growth? And how can targeting any of those processes lead to better outcomes for pancreatic cancer patients?

These questions are components of the broader research themes on which Lyssiotis and Pasca Di Magliano actively collaborate at the Rogel Cancer Center.

Nwosu recently conducted a study to identify genes that show expression differences across multiple pancreatic tumor tissue samples. In that study, published as a preprint on bioRxiv, Nwosu and colleagues identified about 4,000 consistent genes across pancreatic ductal adenocarcinoma datasets. More than half of those genes have not been previously studied in this tumor type. Nwosu and his colleagues highlighted 185 upregulated genes that could be potential therapeutic targets.

The authors call their findings an "important milestone in the quest for mechanisms, drug targets and biomarkers" in pancreatic cancer.

Nwosu first met Lyssiotis at a conference in Spain. At the time, Nwosu was pursuing a doctorate in molecular and cellular biology at the University of Heidelberg in Germany. He was at the conference to present a poster of his work on liver cancer genomics.

Lyssiotis viewed the poster and disagreed with one of Nwosu's findings. It was a spirited but collegial discussion that made a positive, lasting impression. So, when Nwosu was looking for a place to do his postdoctoral training more than a year later, he remembered Lyssiotis and reached out.

"But Michigan? I'm not entirely sure I want to go there," he recalls thinking. "I didn't know much about U-M, but then I looked at Costas's publication record and said I want to work with him."

In addition, he saw U-M as a place where he could advance his interest in cancer metabolism. It's an area the Lyssiotis lab and others at the Rogel Cancer Center are looking to as a potential target to exploit, particularly for cancer types like pancreatic cancer, which have so far been resistant to immunotherapy or targeted therapies. If researchers fully understand what makes cancer cells metabolically different from normal cells — for example, their nutrient needs — they might be able to exploit this knowledge to identify better drug targets and effective therapies.

Nwosu has worked on several projects in both his mentors' labs and has lent his expertise to studies led by other faculty members on colorectal cancer, melanoma, Ewing sarcoma and glioblastoma. Ultimately, Nwosu plans to pursue an independent faculty position that would enable him to continue his work on cancer while also training others.

Pancreatic cancer is a challenging disease. The five-year survival rate hovers around 10%, and many of the advances that have fueled progress in other cancer types are currently ineffective against pancreatic cancer.

Nonetheless, Nwosu sees hope.

"You may have to do 100 things for 10 to be successful. Therefore, if you think too much about the failures, you're never going to succeed. So now your motivation is looking for successes," he says.

Photo: Erica Bass

Probing a Cancer Paradox

Studies kept finding people diagnosed with cancer are less likely to develop dementia — Lindsay Kobayashi was determined to find out if it was true

By Ian Demsky

Epidemiologist **Lindsay Kobayashi, Ph.D.**, doesn't traffick in small numbers. To her, studies with fewer than 1,000 people are modest. And, as an ultramarathon runner, regular marathons of just 26.2 miles are on the shorter side of races she's run — like the 55-mile trek between Durban and Pietermaritzburg in South Africa.

So, it's not surprising that to probe an enduring paradox in cancer and aging, she and her collaborators conducted a systematic review and meta-analysis of 22 studies representing some 9.6 million individuals.

"There's a growing population of people who are older, who have survived cancer and who are expected to live for many more years," says Kobayashi, an assistant professor in the University of Michigan School of Public Health. "We're using the tools of science, statistics and quantitative methods — but ultimately, we're interested in understanding people, and the causes of why some people get sick and others don't."

Alzheimer's disease and related dementias share common risk factors with cancer — with age being the biggest one, she explains. And many treatments for cancer, including surgery and several chemotherapies, are known to have a negative effect on cognition. So, it's counterintuitive that multiple studies have found cancer survivors are less likely to develop dementia than the general population.

"When science presents these kinds of paradoxes, it's important to study them," says Kobayashi, who completed a David E. Bell postdoctoral fellowship at the Harvard T. H. Chan School of Public Health before joining U-M in 2019.

If it's true, that would be an important finding with implications for understanding the causes of both conditions. And if it's not true, identifying the underlying bias or error will improve the design of future studies.

Lindsay Kobayashi, Ph.D., is helping Rogel researchers answer big questions about cancer and aging.

Kobayashi and her colleagues identified six potential forms of bias that could be affecting previous analyses — such as individuals who developed cognitive impairment prior to a cancer diagnosis not being excluded from a study.

Kobayashi's team confirmed that cancer survivors had an 11% lower incidence of dementia than people who never had cancer, according to findings they published in *JAMA Network Open*. However, most of the studies they analyzed suffered from at least one form of bias, the impacts of which they were able to quantify through meta-regressions.

"We're using the tools of science, statistics and quantitative methods — but ultimately, we're interested in understanding people, and the causes of why some people get sick and others don't."

Lindsay Kobayashi, Ph.D.

Two possibilities couldn't be ruled out.

First, survival bias — that is, people who are healthier to begin with are more likely to fare better after a cancer diagnosis and, for the same reasons, also are less likely to develop Alzheimer's.

Second, there could also be a still-unknown biological factor at play that influences the trajectories of both carcinogenesis and neurodegeneration. Genetic epidemiologists continue to investigate this possibility, she notes.

Meanwhile, Kobayashi's larger efforts have focused on providing other Rogel Cancer Center members across U-M with improved access to robust datasets to study big questions in cancer and aging — like how cancer treatments affect cognitive health at a population level.

"We're linking nationally representative datasets with thousands of records and years of longitudinal history, like the U.S. Health and Retirement Study, to Medicare data that includes cancer diagnosis and treatment information," she says. "By allowing us to ask better questions, these tools get us closer to our bigger goal of improving healthy aging outcomes for the growing population of older cancer survivors."

Photo courtesy of the U-M School of Public Health

Let's Talk About How We Talk About Race

Inclusive clinical trials are a must, and we have to get better at articulating why

By Lori J. Pierce, M.D.

History has its eyes on us.

That was one of the key messages in my presidential address at the 2021 annual meeting of the American Society of Clinical Oncology. Institutional racism is finally being recognized as a societal plague that is devastating to all of us — and as physicians and researchers, we must do more to confront the longstanding inequities that pervade oncology and all of medicine.

I made equity for every patient, every day, everywhere the theme of my presidential year, and championed measures to improve access, lower costs and increase the diversity of our workforce.

Improving the racial diversity of our clinical trials is a vital component of this larger effort. And it's important for us to speak clearly about why — or risk reinforcing public misperceptions about race.

"Decades of analyses have shown that 'racial groups' are defined by societies, not by genetics," public health geneticist Alice B. Popejoy, Ph.D., noted in a recent *Nature* editorial. "Only the privileged have the luxury of opining that this is not a problem."

Yet millions of Americans see race as primarily biological in origin rather than as a societal and historical construction. Moreover, white individuals are significantly more likely to believe that racial identity is "determined by information contained in their DNA" than are members of minority communities, according to a national poll by Northwestern University's Center for the Study of Diversity and Democracy and 23andMe.

This kind of thinking can lead to profound misunderstandings about the nature and causes of racial and ethnic disparities in health outcomes — the kind that we've seen tragically underscored by the COVID-19 pandemic.

That means it's imperative that we in the oncology community — and the broader medical community — communicate thoughtfully and with nuance as we pursue efforts to ameliorate these longstanding inequalities.

Let's look at Black Americans specifically.

Black people make up more than 13% of the U.S. population and yet comprise fewer than 5% of participants in most cancer clinical drug trials. There are many reasons for this gap — including lack of access, lower rates of insurance, financial barriers and an enduring mistrust of the medical research establishment.

At the same time, for most cancers, Black patients have higher death rates and shorter lengths of survival than members of other racial and ethnic groups, American Cancer Society statistics show.

These disparities need to be discussed and addressed.

Race can be a challenging subject to talk about. And I'm encouraged by how the important and sometimes painful conversations that are currently happening in the halls of medicine are part of a larger reckoning happening across the country on issues of race and justice.

So, when we talk about the importance of increasing racial diversity in our clinical trials, we must be careful not to reinforce false beliefs about race at the same time.

Why *do* we want to increase the participation in clinical trials among Black, Hispanic/Latinx and other minority patients with cancer?

First and foremost, these populations deserve access to cutting-edge investigational treatments that may improve or extend their lives. It's a fundamental component of high-quality cancer care.

Second, the greater the diversity among clinical trial participants and the better it reflects the overall diversity of our patients, the better we can identify important differences in outcomes between groups.

But let's be clear: Only a small fraction of the difference between racial groups is genetic. At that level, humans are 99.9% identical. Social determinants of health play a far greater role — factors like access to nutritious food, economic stability, safe housing and neighborhoods, education and job opportunities, and exposure to environmental pollution.

Race is a cultural category through which we can see the history of these factors at play. And they are the levers by which institutional racism continues to affect health outcomes.

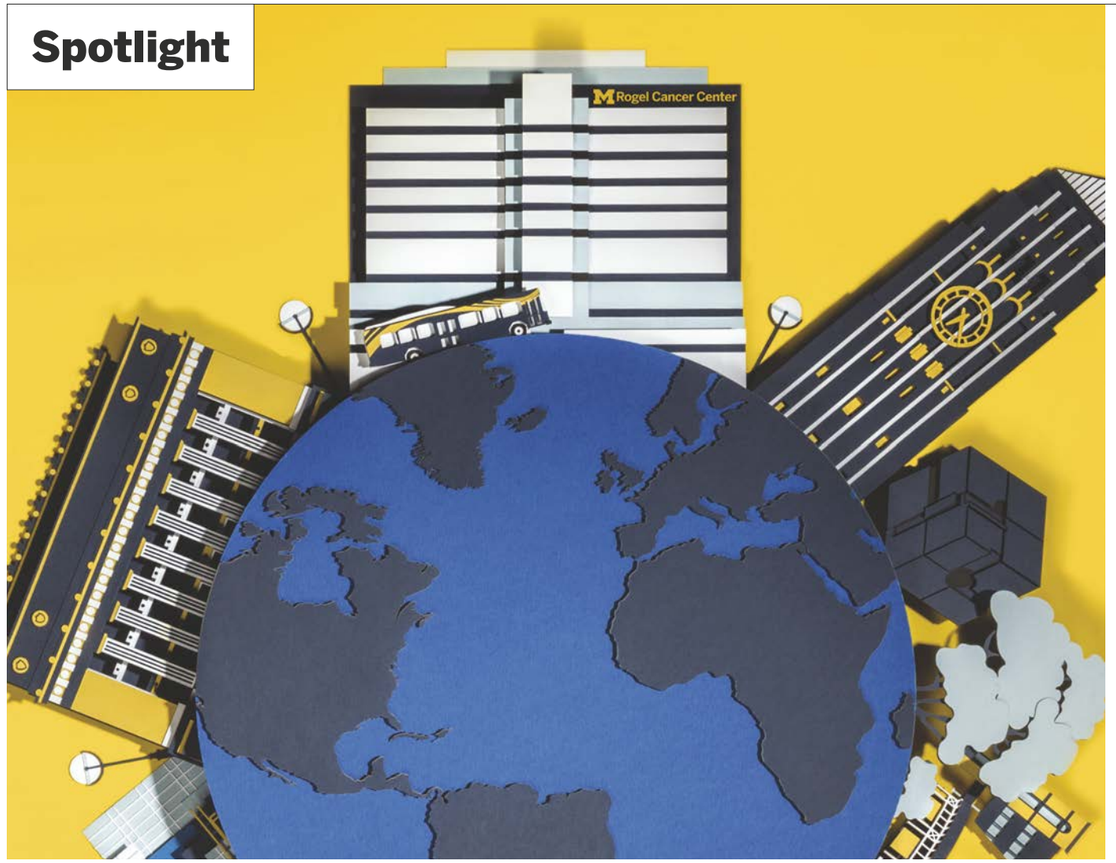
"The causes of these inequalities are complex and reflect social and economic disparities and cultural differences that affect cancer risk, as well as differences in access to high-quality care, more than biological differences," the ACS's Cancer Facts and Figures for African Americans 2019-2021 appropriately notes.

So, if we simply state to the public that we want to increase the diversity of clinical trial populations to better understand how well treatments work or don't work for different racial groups, we do a disservice. While that is true at a surface level, it is not the whole truth.

Ultimately, increasing diversity in clinical trials is not meant to provide a better accounting of racial differences, but rather to *provide an antidote* to years of structural racism.

This is the message I urge all of us to convey — boldly, yet thoughtfully — as part of our ongoing commitment to health equity.

***Lori J. Pierce**, M.D., is professor of radiation oncology at Michigan Medicine and vice provost for academic and faculty affairs at the University of Michigan. She served as the 2020-2021 president of the American Society of Clinical Oncology.*



NCI Funding to Rogel Up By Nearly 40% since 2015

Over the past six years, funding to the Rogel Cancer Center from the National Cancer Institute rose by 38% to nearly $78 million, placing the center sixth in the nation.

This prodigious growth reflects hard work and commitment across the entire organization to patient care, cancer research and the education of trainees, says **Julie Brabbs, M.B.A.**, the cancer center's chief administrative officer.

Rogel Team Receives $11.2M to Leverage the Microbiome Against GVHD

Pavan Reddy, M.D.

A team of Rogel researchers received an $11.2 million grant from the National Heart, Lung and Blood Institute to study how to use the microbiome to limit graft-versus-host disease, a complication of stem cell transplants for blood cancers and other diseases.

"Our overarching goal is to make allogeneic hematopoietic cell transplantation safer and more efficacious," says principal investigator **Pavan Reddy, M.D.**, deputy director of the cancer center and division chief of hematology/oncology. "The proposal has a unifying central theme to understand the role of intestinal microbial metabolite interactions with host metabolism and the impact on intestinal GVHD."

Four funded projects will explore: crosstalk between host cells and the metabolite butyrate in mouse models of GVHD, led by Reddy; host-microbiome interaction involving secondary bile acids, led by **Gabriel Nuñez, M.D.**; critical microbes and mechanisms that break down resistant starch to generate butyrate and secondary bile acids, led by **Thomas Schmidt, Ph.D.**, and **Nicole Koropatkin, Ph.D.**; and a proof-of-concept clinical trial looking at the role of dietary resistant starch on patients' microbiome and metabolome, and the impact on clinical GVHD, led by **Muneesh Tewari, M.D., Ph.D.**, and **Mary Riwes, M.D.**

Illustration: Phil Zhang, courtesy of U-M Office of University Development

$13M Grant Will Track Cancer Risk From Environmental Exposures

A new study from University of Michigan School of Public Health and Rogel Cancer Center researchers will describe and quantify the impact of known and suspected environmental exposures on cancer risk. The program, called MI-CARES — for Michigan Cancer and Research on the Environment Study — is funded through a $13 million grant from the National Cancer Institute.

"Many communities experience a disproportionate disease burden because of failed governmental stewardship of local environments and the prioritization of private enterprise over health protection. With growing awareness of the health threats of these decisions, it's essential to put greater focus on environmental contaminants and public health safety," says principal investigator **Celeste Leigh Pearce, Ph.D., M.P.H.**, a professor of epidemiology at the U-M School of Public Health.

MI-CARES will enroll at least 100,000 people from diverse racial and ethnic backgrounds who live in environmental hotspots throughout Michigan including the Detroit metropolitan area, Flint, Grand Rapids, Kalamazoo, Lansing and Saginaw. Enrollment will be open to all Michiganders ages 25-44. Participants will be followed over time through surveys as well as blood and saliva samples to track environmental exposures and cancer biomarkers.

Cancer Prevention Trials Get Boost From $7.2M NCI Grant

Dean Brenner, M.D.

A $7.2 million grant from the National Cancer Institute will allow Rogel researchers and their national collaborators to test whether blocking inflammation could protect cells and potentially prevent some cancers.

"Our overarching hypothesis is that the cellular shifts caused by inflammatory processes can be reversed or dampened by clinical preventive agents. With this grant, we'll develop early phase clinical trials with new, less toxic agents in the hopes that this approach can ultimately reduce cancer deaths," says **Dean Brenner, M.D.**, the Moshe Talpaz M.D. Professor of Translational Oncology and professor of internal medicine and pharmacology.

Brenner and **Zora Djuric, Ph.D.**, a research professor of family medicine and nutrition sciences, are dual principal investigators on the grant. They have formed the Early Phase Clinical Cancer Prevention (ClinCaP) Consortium, which includes investigators from nine other NCI-designated centers.

"We have a specific focus on obesity, which is a key source of inflammation," Djuric says. "There is tremendous opportunity to stop or alter these obesity-driven processes and potentially prevent cancer from developing."

Lori J. Pierce, M.D., delivers her ASCO Presidential Address at the Michigan League.

Photo: Bryan McCullough

ASCO Honors and Special Awards

Lori J. Pierce, M.D., served as the 57th president of the American Society of Clinical Oncology and made the theme of her 2020-21 presidential year "Equity: Every Patient. Every Day. Everywhere." Pierce, a professor of radiation oncology, was the first Black woman to serve in the role.

N. Lynn Henry, M.D., Ph.D., an associate professor of internal medicine, served as the annual meeting's scientific committee chair.

Rogel members **Arul Chinnaiyan, M.D., Ph.D.**, and **Daniel Hayes, M.D.**, also received special recognition from ASCO last year. Chinnaiyan, the S.P. Hicks Endowed Professor of Pathology, received the Science of Oncology Award and Lecture, recognizing outstanding contributions to basic or translational research in cancer. Hayes, the Stuart B. Padnos Professor of Breast Cancer Research, received the Allen S. Lichter Visionary Leader Award and Lecture, which recognizes ASCO members who have transformed the oncology field through their leadership, vision and ability to inspire.

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

Daniel Hayes, M.D.

N. Lynn Henry, M.D., Ph.D.

Friese Appointed to National Cancer Advisory Board

President Joseph Biden named **Christopher Friese, Ph.D., R.N.**, among seven new members of the National Cancer Advisory Board.

Friese is the Elizabeth Tone Hosmer Professor of Nursing, Health Management & Policy at the University of Michigan and associate director for cancer control and population sciences at the Rogel Cancer Center.

Friese is a national expert in the analyses of claims data to study care quality and has executed large surveys of ambulatory oncology nurses. He leads an interdisciplinary research program to study the quality of care delivered in understudied ambulatory oncology settings from the perspectives of patients and clinicians.

The National Cancer Advisory Board is an elite group of 18 cancer clinicians and researchers who play an important role in guiding the director of the National Cancer Institute in setting the course for the national cancer research program. Friese's term will last six years.

"I am deeply honored that President Biden has nominated me for the National Cancer Advisory Board," Friese said. "As a nurse scientist and educator, I hope to bring my expertise and insights to advance cutting edge research that will reduce the societal burden of cancer."

Individual Honors

John Ayanian, M.D., M.P.P., **Sarah Hawley, Ph.D., M.P.H.**, **Megan Haymart, M.D.**, **John Voorhees, M.D.**, Distinguished Clinical and Translational Research Mentor Award, Michigan Institute for Clinical & Health Research (MICHR)

Richard Auchus, M.D., Ph.D., Outstanding Clinical Investigator Award, the Endocrine Society

Sally Camper, Ph.D., Sidney H. Ingbar Distinguished Service Award, the Endocrine Society

Robert Dess, M.D., ROI Publication Award, Radiation Oncology Institute

Christopher Friese, Ph.D., R.N., Distinguished Research Award, Oncology Nursing Society

Thomas Giordano, M.D., Ph.D., **Gary Hammer, M.D., Ph.D.**, AACR Team Science Award to The Cancer Genome Atlas (TCGA) team

Megan Haymart, M.D., Woman of the Year, Women in Thyroidology, American Thyroid Association

William Jackson, M.D., Young Investigator Award, National Comprehensive Cancer Network Foundation

Reshma Jagsi, M.D., D.Phil., Woman in Science Award, American Medical Women's Association

Celina Kleer, M.D., Outstanding Investigator Award, American Society of Investigative Pathology

Laurie McCauley, D.D.S., Ph.D., Norton M. Ross Award for Excellence in Clinical Research, American Dental Association

Sunitha Nagrath, Ph.D., elected to the College of Fellows at the American Institute for Medical and Biological Engineering

Phillip Palmbos, M.D., Ph.D., Damon Runyon Clinical Investigator Award (with mentor **Joshi Alumkal, M.D.**)

Maria Papaleontiou, M.D., AACE Rising Star in Endocrinology Award, American Association of Clinical Endocrinology; ASCI Council Young Physician-Scientist Award, American Society for Clinical Investigation

Lori J. Pierce, M.D., Gold Medalist, American Society for Radiation Oncology

Jeffrey Tosoian, M.D., Michael & Patricia Berns-PCF Young Investigator Award, Prostate Cancer Foundation (with mentors **Arul Chinnaiyan, M.D., Ph.D., Todd Morgan, M.D., Bruce Trock, Ph.D.**)

Daniel R. Wahl, M.D., Ph.D., Damon Runyon Clinical Investigator Award (with mentors **Ted Lawrence, M.D., Ph.D.**, and **Maria Castro, Ph.D.**)

Photo: Leisa Thompson

The Art of Science

Only about 1 in 4 patients with bladder cancer sees their tumors respond to immunotherapy. **Phillip Palmbos, M.D., Ph.D.**, an assistant professor of hematology/oncology, is working to understand why. Here, immunofluorescent staining shows ATDC/TRIM29 (purple) in bladder cancer cells. The oncogene is highly expressed in most invasive bladder cancers and may suppress antitumor immunity in patients. Palmbos' lab is investigating the mechanisms by which it causes resistance to therapy and ways to sensitize tumors to treatment. ***Image by Yin Wang Ph.D***

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