Illuminate

UNIVERSITY OF MICHIGAN HEALTH ROGEL CANCER CENTER 2023

Hitting the Mark

Also: Understanding metabolic pathways; collaboration during COVID-19

UNIVERSITY OF MICHIGAN HEALTH ROGEL CANCER CENTER **2023**

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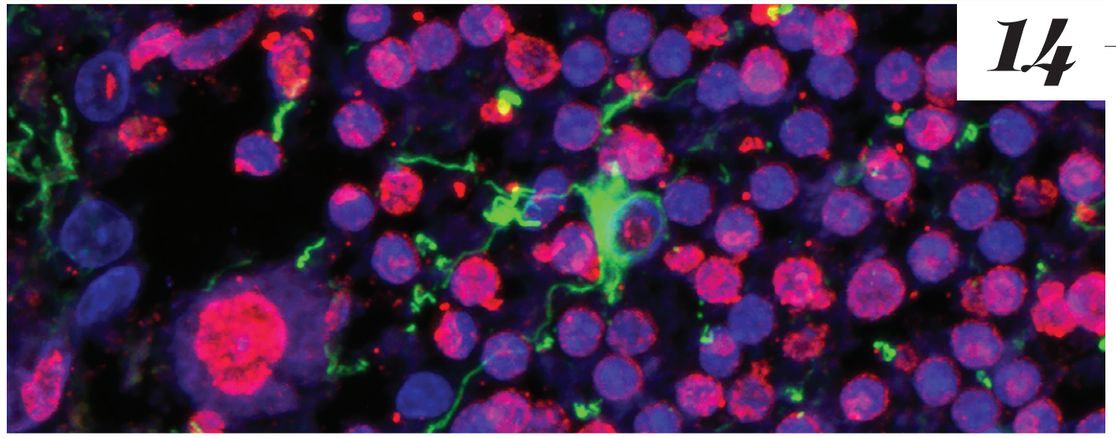

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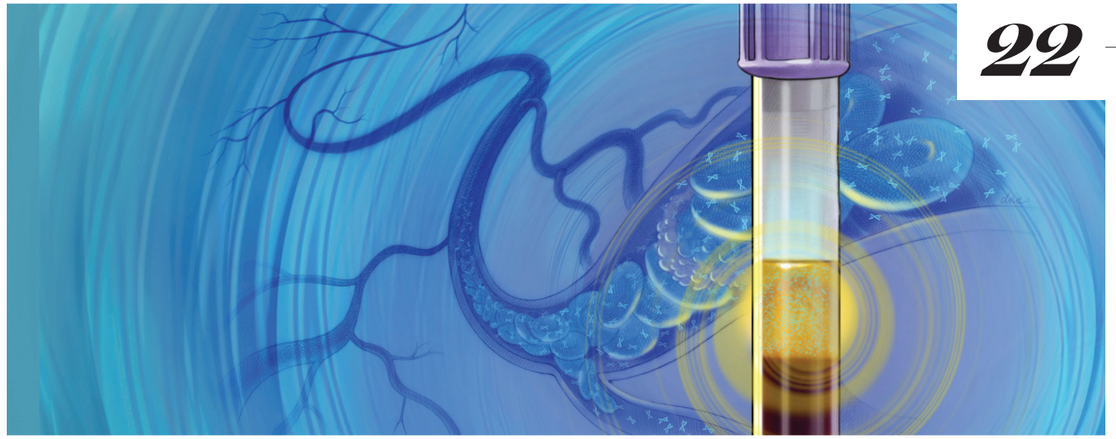

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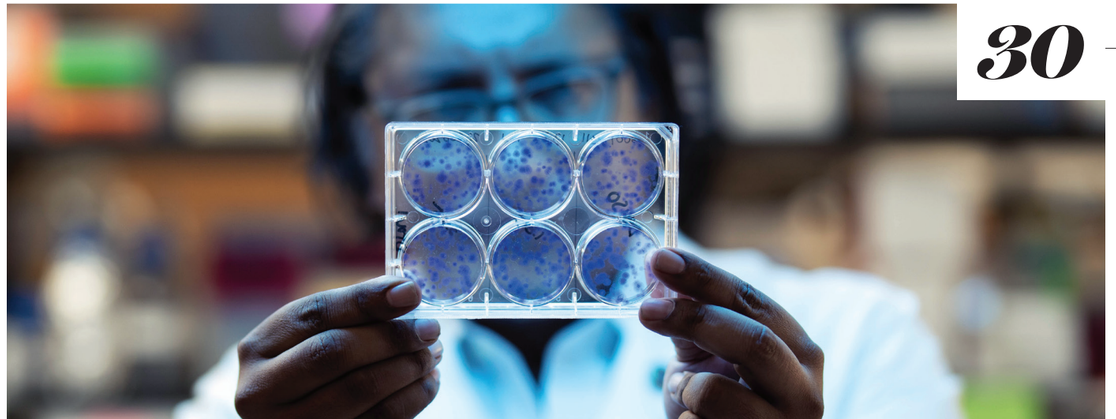

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FEATURES

Hungry for More

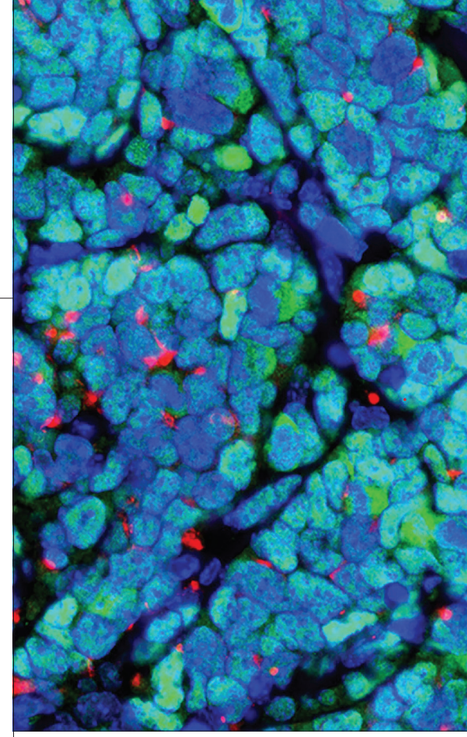
Metabolism pathways make tumors sensitive or resistant to treatments. A collaborative group of Rogel researchers is leveraging these avenues to explore the growing foundation of new potential therapies.

Hitting the Mark

Circulating biomarkers, a new frontier in cancer care, bring both hope and unease to the clinic. Rogel researchers are unraveling their nuances, advancing enabling technologies, advocating for patients and figuring out how to ethically integrate this technology into clinical care.

Problem Solvers

When the pandemic hit, Rogel researchers, clinicians and staff needed to rethink how they did their work. In doing so, they discovered new ways to fulfill the cancer center's mission despite unprecedented uncertainty.



Published annually by the University of Michigan Health Rogel Cancer Center, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-5944. If you have questions or a story idea for Illuminate, please email Anna Megdell at megdella@med.umich.edu.

ROGEL CANCER CENTER
UNIVERSITY OF MICHIGAN HEALTH

About Us

333
members

across
9
schools & colleges

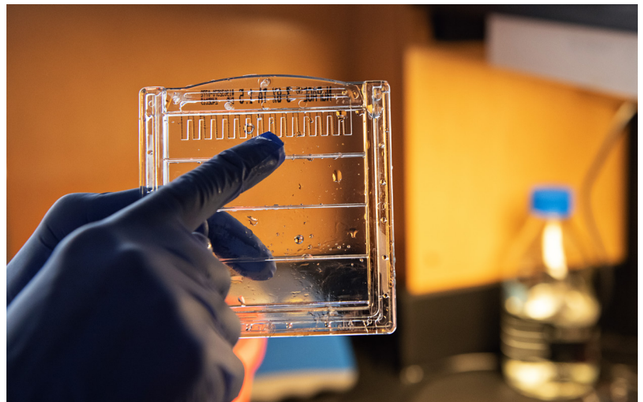
and
54
departments

1,301
annual publications

1,771
yearly clinical trial accruals

$170M
grant funding

No. 9
National Cancer Institute funding



Director's Letter

Dear Colleagues,

This past year, the Rogel community has taken stock of who we are—as scientists, clinical care providers, learners and collaborators. As we continue to adjust to a world changed by the COVID-19 pandemic and evolve the ways we work, I'm struck by the abundance of creativity, innovation and deep commitment to all aspects of the cancer problem in our community.

Our community's energy and passion were top of mind as we put together our Cancer Center Support Grant renewal in spring 2022 and prepared for our NCI site visit last fall, efforts that required us to review our work, research and initiatives, and tell the story of who we are as a comprehensive cancer center. And we did. We displayed the remarkable breadth and depth of our research, from the lab to translational research to clinical care and population sciences research. We developed robust plans to support the next generation of cancer researchers and to address the most crucial health care needs of our statewide community. We also identified key areas in which we want to grow. We demonstrated our commitment to advancing DEIJ impact across all Rogel missions.

Throughout the massive undertaking of submitting the CCSG and preparing for the site visit, one thing crystalized: the collaborations among colleagues from diverse units across U-M is the life source of this institution. It is what sustains us, what inspires us and what keeps us pushing research forward for the benefit of patients, survivors and all at risk of cancer.

The pages of this year's *Illuminate*, the third issue of our research magazine, demonstrate our collaboration and interconnectedness, and highlight the range and depth of Rogel's research. In this issue you'll read about a working group focused on understanding how metabolism can offer new hope for cancers that have been unresponsive to treatment, work that spans across disciplines and requires collaboration at every level. You'll also read some of our faculty's thoughts about circulating biomarkers and liquid biopsies, technologies which open possibilities of tracking recurrence while simultaneously raising ethical questions about how cell-free DNA can, and should, be used to test for cancer in otherwise healthy patients. Rogel faculty give a wraparound perspective to this topic, presenting a framework in which to ask the right questions.

The third feature hits at the heart of this theme, telling the story of how Rogel continued its vital collaboration during the height of the COVID-19 pandemic, a time when we were forced to isolate and fundamentally pivot our work. We see the tenacity, creativity and care behind these changes, and what it means for our faculty and trainees.

Collaboration is not one-dimensional. By nature it is dynamic and ever-changing. So is Rogel, as demonstrated by the changes of the last few years and the clarity with which we understand our strategic goals and commitments. Our members, staff and trainees are deeply connected and interdependent, and the stories in this issue highlight the ways in which our work is as well. May we continue to work together, to push the boundaries of scientific knowledge and to continue to show up for one another. The urgent needs of our patients and survivors for further improvements in cancer care, outcomes and quality of life implore us to follow what is most often cited as an African proverb—"If you want to go fast, go alone; if you want to go far, go together."

Sincerely,

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

Photo: Erica Reist Bass

Discoveries

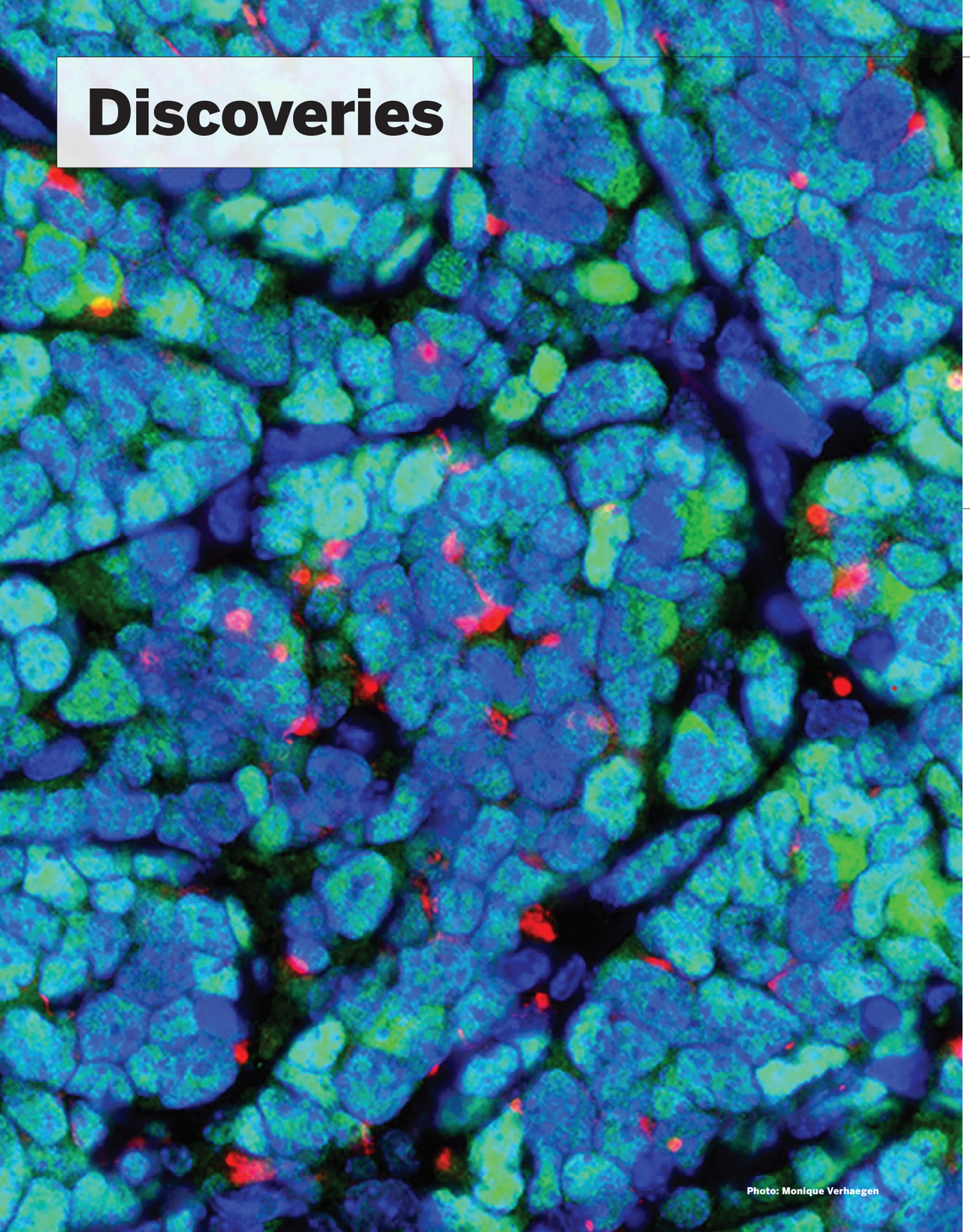


Photo: Monique Verhaegen

Viral proteins key to tumor model in mice

MOLECULAR DETERMINANTS ↔ A team of Rogel researchers was the first to generate a bona fide mouse model of a Merkel cell carcinoma, a rare and potentially aggressive form of skin cancer. The study outlining these results appeared in the *Journal of Clinical Investigation*.

Scientists have been working to make a mouse model of this tumor to better understand the disease biology to support preclinical testing of novel drugs, but no one before has been successful. A Merkel cell polyomavirus is believed to cause about 80% of these tumors, but researchers have been unable to definitively show this in vivo.

"We've been working on this for 10 years," says **Monique Verhaegen, Ph.D.** One of the roadblocks to this discovery lay in the cell of origin for Merkel cell carcinoma. "Nobody knows what it is, so we didn't know what cell to manipulate to see if it could grow into a tumor," Verhaegen explains.

This changed when the team, led by Verhaegen and **Andrzej Dlugosz, M.D.**, discovered one more piece to the puzzle: the deletion of the tumor suppressor p53 alongside the expression of the viral proteins. This finally led to a full-blown tumor in a mouse model, one that was visible on the skin and mimicked human Merkel cell carcinoma at the histological, marker expression and transcriptomic levels. "When we saw that, we knew we had a real tumor," Verhaegen says.

Healthy microbiome, metabolites protect against colorectal cancer

MICROBES & IMMUNITY ↔ An imbalance in the gut microbiome is a hallmark of colorectal cancer, contributing to inflammation, tumor growth and response to therapy. A study led by **Yatrik Shah, Ph.D.**, finds a healthy microbiome and a specific metabolite called reuterin can protect against colorectal cancer.

The study, published in *Cancer Cell*, found that microbial metabolites from healthy mice or humans repress cell growth—a response that's heightened in mice and humans with colorectal cancer.

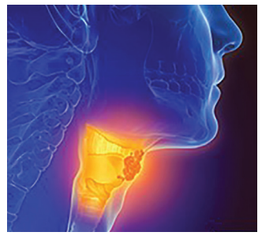
The team profiled the microbiome and identified Lactobacillus reuteri and its metabolite reuterin are downregulated in colorectal cancer. When reuterin was increased, it reduced the growth and survival of colon cancer cells. Studies have shown high doses of reuterin are well-tolerated.

The finding suggests potential for L. reuteri and reuterin to be used in combination with traditional colorectal cancer therapies or even as a prevention strategy.

Left: Mouse tumor of Merkel cell carcinoma stained to show specific markers.

Two markers help predict head and neck cancer prognosis

BIOMARKERS ↔ A new study from **J. Chad Brenner, Ph.D.**, in *Clinical Cancer Research* finds circulating tumor DNA, or ctDNA, levels can predict as early as two weeks after starting treatment which patients are likely to have good outcomes.



"Rates of throat cancer have steadily increased in recent years, driven by HPV infections, fueling the need for biomarkers to help guide treatment decisions, especially for locally advanced disease," Brenner says.

"Quantitative imaging of metabolism, local blood volume density and cell density from PET and MRI scans have shown both prognostic value in predicting treatment outcome as well as utility in selecting patients for additional focal radiation treatment," says study author **Yue Cao, Ph.D**.

The researchers conducted a randomized trial of patients with stage 3 oropharyngeal squamous cell carcinoma. In total, 93 patients had imaging and 34 also had blood tests before starting chemoradiation and again at two, four and seven weeks after treatment.

The study found that HPV ctDNA clearance at two weeks, but not at four weeks, predicted outcomes. The metabolism, local blood density and cell density before radiation therapy or at two weeks after starting treatment predicted outcomes as well. These early predictor biomarkers could help determine which patients need more aggressive treatment. A larger study is needed.

Study demonstrates a novel approach to target enhancer-reliant cancers

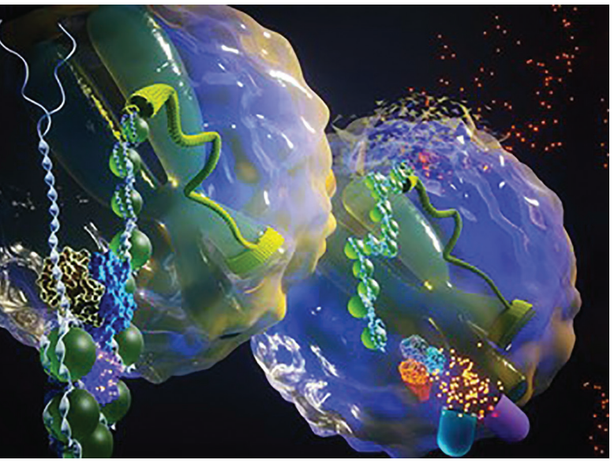
GENETICS ↬ While researchers have identified several genes that drive prostate cancer, a new study published in *Nature* reveals the puppet master controlling the strings.

Rogel researchers demonstrated that the SWI/SNF complex facilitates access to enhancers that oncogenes can bind to and drive downstream gene expression in cancer. Degrading a subunit of this complex blocks the oncogenes, like cutting the puppet master's strings.

The finding reveals a novel approach to treating prostate cancers fueled by different genetic drivers, which altogether represent upwards of 90% of all prostate cancers.

In human cells, DNA is tightly wrapped around histone proteins, collectively referred to as chromatin. These form a physical barrier to all DNA-based processes. Specialized protein machineries have evolved that consume energy and modulate the physical state of the DNA for its functional activation. These complexes work in close concert with DNA-binding regulatory factors called transcription factors to impart distinct cellular identity and function.

"This is the first demonstration in cancer that blocking access to chromatin can be pursued as an avenue to treat cancer. By compacting the chromatin around these enhancer elements, transcription factors are blocked from binding to the enhancer elements that drive cancer," says study author **Arul M. Chinnaiyan, M.D., Ph.D.**



New clues to how the tumor microenvironment impacts pancreatic cancer

TUMOR MICROENVIRONMENT & METABOLISM ↬ In a study published in *eLife*, Rogel researchers looked at the mitochondrial metabolism, which is a key driver of pancreatic cancer.

By looking at cell lines, they found loss of mitochondrion GOT2 causes metabolic changes that impair cellular growth. But in engineered mice, loss of GOT2 had no effect on tumor growth or initiation.

Cancer cells use a complex cell-intrinsic rewiring and crosstalk with the tumor microenvironment in vivo. These data emphasize an under-appreciated role for GOT2 in pancreatic tumor redox homeostasis and illustrate the way cancer cells use biochemical pathways and metabolic plasticity to grow in vivo. The study was led by **Costas Lyssiotis, Ph.D.**, and **Yatrik Shah, Ph.D.**

Physicians don't always recognize radiation therapy side effects

HEALTH EQUITY ↬ Physicians did not recognize side effects from radiation therapy in more than half of breast cancer patients who reported a significant symptom, a new study in *JAMA Oncology* finds.

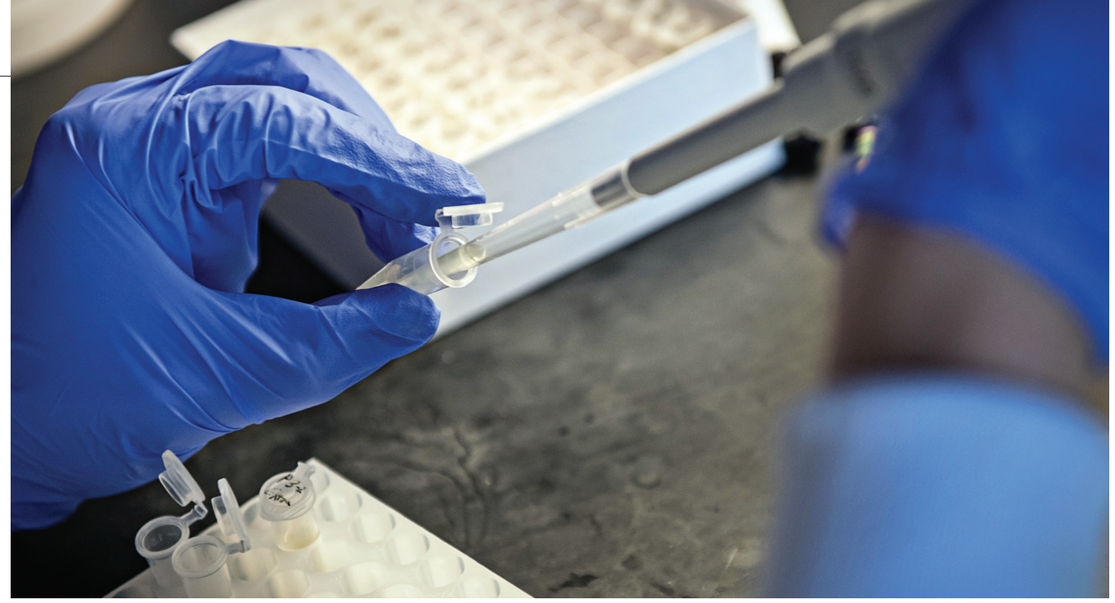
The Rogel study compared reports from almost 1,000 patients from practices across the state of Michigan who received radiation therapy following lumpectomy. Patients filled out standard symptom reporting tools for four common side effects during their radiation treatment: pain, itchy skin, swelling and fatigue. At the same time, physicians assessed patients' symptoms using a standardized tool called the Common Toxicity Criteria for Adverse Events.

Researchers compared these two sets of symptom reports and found incidences where physicians reported no issue even though patients reported substantial concerns. This under-recognition occurred in 31% of patients reporting pain, 37% of patients with itchy skin, 51% of patients with swelling and 19% of patients with fatigue.

The study, led by Rogel researchers including **Lori J. Pierce, M.D.**, and **James A. Hayman, M.D., M.B.A.**, found that side effects were more likely to be missed in younger patients and Black patients, suggesting that better methods to detect symptoms in these patients could help reduce disparities in patient experiences and outcomes.

The team proposes additional research to understand why certain populations are more likely to have symptoms missed and how to overcome any issues of misconception or mistrust between patients and providers.

Illustration: Ella Maru Studio



Study suggests commonly used prostate cancer treatment rewires engine of prostate tumors

THERAPEUTICS ↬ Drugs like enzalutamide that inhibit male hormones from activating the androgen receptor have been used to treat advanced prostate cancer for more than a decade. While successful in most cases, these drugs can eventually stop working—but there is a limited understanding about how this change occurs.

A new study from **Joshi Alumkal, M.D.**, suggests androgen receptor inhibitors can fundamentally rewire and reshape how prostate tumors function, and in certain cases even make them more aggressive. These findings were published in *Nature Communications*.

"The greatest unmet need in the clinic right now is understanding the workarounds in a tumor that becomes resistant to androgen receptor targeting drugs so we can determine how best to treat the patient whose tumor has begun to grow," Alumkal says. "Once enzalutamide stops working, there are limited options. We don't know how or why most tumors become resistant."

He and colleagues recruited patients to a longitudinal study to obtain metastatic biopsies before enzalutamide treatment and at the time the tumor became resistant to treatment. His team collected serial biopsies from 21 patients, enabling them to understand the workarounds in the tumor from each patient.

In three of the 21 cases, Alumkal and his team saw a profound shift in the wiring—or gene expression program—of the tumors.

Alumkal uses vehicles to describe this change.

"Initially, nearly all prostate tumors are gas guzzlers: very fuel dependent and powered by the androgen receptor as the engine. When treated with hormonal treatments, most tumors remain fuel-dependent but become more fuel efficient, able to go farther with less gasoline.

"Our work showed that the majority of the tumors—even after receiving enzalutamide—remain very fuel-dependent, which suggests that continuing to target the androgen receptor could make an enormous difference in these tumors," Alumkal continues.

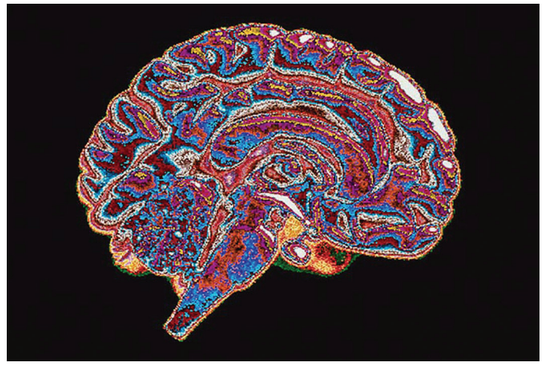
Researchers find link between genetic mutations and cancer treatment resistance

GENETICS ↬ Studying the molecular landscape of over 500 patients with an aggressive form of multiple myeloma, Rogel researchers discovered a prevalence of activated key oncogenic pathways, much more than previously thought. The study, published in *Nature Communications*, found that upwards of 45%-65% of NF-κB and RAS/MAPK pathways each had alterations.

The team compared the molecular makeup of patients with untreated multiple myeloma to those with the relapsed treatment-resistant version of the disease. Comparing these patients allowed researchers to describe drivers of the more aggressive form of multiple myeloma.

"It also led us to discover resistance mechanisms that occur in the patients whose disease relapses and is resistant to treatment," says **Arul M. Chinnaiyan, M.D., Ph.D.** "We found that upwards of a quarter of the patients had developed some sort of resistance mechanism. The genetic alterations that occur in these patients make them resistant to commonly used treatments of multiple myeloma."

Photo: Erica Reist Bass



New clues toward treating pediatric brain tumors harboring epigenetic mutation

MOLECULAR DETERMINANTS; GENETICS ↬ While substantial strides have been made against some types of childhood cancers, high-grade gliomas still lack effective treatments.

Thirty to 60% of these pediatric brain tumors bear mutations in the gene H3F3A. This gene contains the encoded blueprint for histone H3.3, which plays an important role in the structure of chromatin. One of these mutations is known to scientists as H3.3G34R/V—meaning the amino acid glycine that's normally found at position 34 has been replaced by either an arginine or a valine.

Now an international team led by Rogel researchers has found a small-molecule inhibitor that was able to suppress tumor growth in animal models of this glioma—offering new hope toward developing therapies for pediatric patients. Their findings appear in *Science Translational Medicine*.

"These tumors tend to occur in slightly older children than some of the more well-known types of childhood glioma—usually between the ages of 10 and 18," says senior author **Sriram Venneti, M.D., Ph.D.** "And the prospects remain quite dismal due to a lack of effective treatments."

Led by graduate student **Stefan Sweha**, the team investigated epigenetic changes to the tumors—that is, changes that are not permanent mutations to the DNA itself, but which affect how cells access and read DNA sequences. Ultimately, they found alterations that led to increased secretion of a protein known as LIF, for leukemia inhibitory factor. LIF, in turn, activates the STAT3 signaling pathway, which has been implicated in a number of other types of cancer.

In mouse models of H3.3G34R/V glioma, a small-molecule inhibitor of STAT3 called WP1066 was shown to suppress tumor growth and greatly improve how long the mice survived.

"Our goal is to move the compound into clinical trials for pediatric patients," Venneti says.

Researchers find natural mechanism to sensitize cancer to immunotherapy

MICROBES & IMMUNITY ↬ Rogel researchers found that a cytokine, a category of protein that acts as messengers in the body, and a fatty acid can work together to trigger a type of cell death previously defined by studies with synthetic molecules.

The study, published in *Cancer Cell*, looked at cell cultures and in vivo mouse experiments to see how the release of the T cell cytokine interferon gamma combined with arachidonic acid, a fatty acid, leads to a type of cell death called ferroptosis via targeting the enzyme ACSL4. Ferroptosis has been found to occur in tumor cells and plays a role in cancer immunity. Understanding how ferroptosis occurs could open pathways to make immunotherapy treatments more effective.

"Targeting ACSL4 may help in understanding and expanding possible immunotherapy options," says **Weiping Zou, M.D., Ph.D.**

Zou explains that this natural mechanism begins when activated T cells release interferon gamma, a signaling protein. "It's well known that interferon gamma is involved in anti-tumor responses," says Zou. "But in this study, we defined a new way that it works."

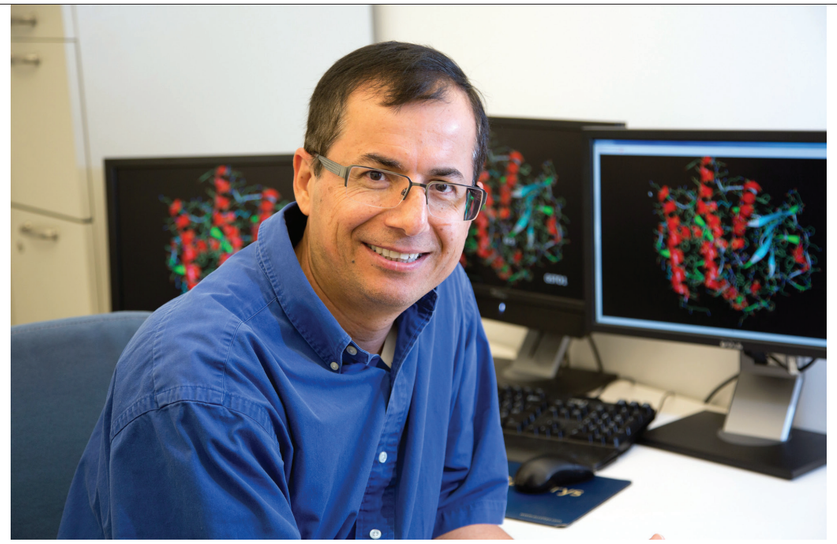
This study shows that combining interferon gamma with arachidonic acid, a fatty acid found in the tumor microenvironment, activates ACSL4, alters tumor cell lipid pattern and naturally induces tumor cell ferroptosis. "ACSL4-dependent tumor ferroptosis is a mode of action of killer T cells," says Zou. "Targeting ACSL4 sensitizes cancer to immunotherapy."

Zou's lab was the first to identify a role for ferroptosis in cancer immunity and therapy, highlighting the possibility of targeting this pathway to improve the effectiveness of immunotherapy in people with cancer. While immunotherapy has dramatically changed outcomes in melanoma, lung cancer and other cancer types, the treatments work for only about 30% of people with cancer.

These new findings add more knowledge to how ferroptosis works in patients with cancer, which Zou hopes will prompt further investigation.

"This study raises a lot of questions for us to keep exploring, particularly around the basic biology of cell ferroptosis, including the involvement of different fatty acids and dietary lipids, the different roles immune cells play in ferroptosis and how to target ACSL4 and ferroptosis pathways," Zou says. "For now, there are many unknowns, but we'll continue to work in this space."

Photo: Getty Images



A team of Rogel researchers led by Nouri Neamati, Ph.D., (left) screened some 4,000 compounds to identify a lead candidate that shows potency as an OXPHOS inhibitor.

Researchers ID promising new inhibitor against pancreatic cancer

MOLECULAR DETERMINANTS ↬ Research has suggested blocking oxidative phosphorylation may be a promising metabolic approach to treating select cancers. A team of Rogel researchers led by **Nouri Neamati, Ph.D.**, screened some 4,000 compounds to identify a lead candidate that shows potency as an OXPHOS inhibitor. Their study is published in the *Journal of Medicinal Chemistry*.

Mechanistic studies using pancreatic cancer cells and mouse models showed the lead compound inhibited OXPHOS Complex 1. After an extensive lead-optimization campaign, two compounds were selected that hold potential to be developed into novel drugs targeting pancreatic cancer and other cancers dependent on OXPHOS.

BRCA-positive breast cancer patients are more likely to get aggressive chemotherapy

GENETICS; THERAPEUTICS ↬ Breast cancer patients who test positive for genetic variants in BRCA1 or BRCA2 had twice the odds of those without a genetic variant of receiving platinum chemotherapy as part of a more intensive regiment, according to a study in *JNCI Cancer Spectrum*.

Researchers, led by **Steven Katz, M.D., M.P.H.**, linked SEER registry records from Georgia and California to germline genetic testing results to understand how genetic testing results were influencing chemotherapy regimens. Patients whose cancers were hormone receptor-positive and HER2-negative, were more likely to receive aggressive chemotherapy, while triple-negative breast cancer patients were not.

The authors suggest the aggressive chemotherapy is likely overtreatment and emphasize monitoring how genetic testing results are incorporated into clinical care.

Researchers develop first inhibitors against key epigenetic complex involved in cancer

GENETICS; MOLECULAR DETERMINANTS ↬ Leukemia stem cells are rare cells that can renew themselves while continuing to generate malignant cells known as leukemic blasts. These cells are difficult to eradicate using chemotherapy drugs and frequently lead to recurrence of leukemia.

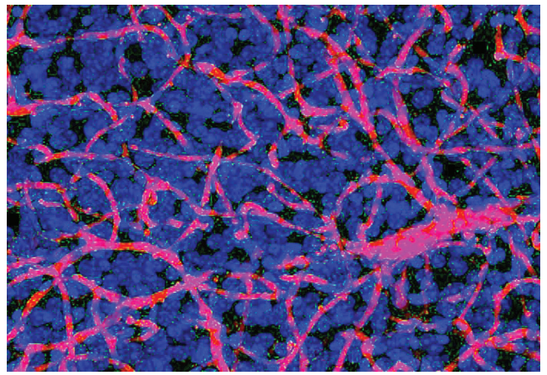
Leukemia stem cells, however, are dependent on a protein complex called polycomb repressive complex 1, or PRC1, which interacts with chromatin and turns genes off.

A team of researchers led by **Tomasz Cierpicki, Ph.D.**, and **Jolanta Grembecka, Ph.D.**, has developed the first small-molecule inhibitors of PRC1—a first step toward developing a potential new therapeutic approach to treating acute myeloid leukemia by shutting down the activity of leukemia stem cells.

These inhibitors demonstrate activity in leukemia cells and patient samples, as reported in *Nature Chemical Biology*, and also open new opportunities to study the development of leukemia at the molecular level.

"Our lead compound, RB-3, represents an attractive and unique agent for studying PRC1 biology," says Cierpicki. "This work demonstrates that directly targeting the activity of PRC1 is indeed feasible and could lay the groundwork for the development of new pharmaceutical agents for leukemia and possibly other cancers."

Photo: Michigan Medicine



For glioma patients, a mutated gene may create new treatment options

GENETICS ↔ A mutation in the protein coding gene ATRX affects growth of brain tumor cells in young adults, indicating sensitivity to a new treatment strategy, a team of researchers led by **Carl Koschmann, M.D.**, discovered. The findings, published in *Cell Reports*, present possibilities for more effective therapies for glioma patients with this gene mutation.

ATRX is mutated in just over half of high-grade glioma young adult patients, but no targeted therapies exist. Researchers found that glioma cells with mutated ATRX have less amount and activity of the protein Checkpoint Kinase 1 (Chk1), which regulates the division of glioma cells.

Radiation generally stops cells from cycling and dividing, and healthy cells and glioma cells will use this time to heal their damaged DNA to maintain the strength of the cell. But those checks aren't in place with ATRX-mutated cells. After radiation, the mutated cells keep cycling and have limited ability to repair their DNA. This makes the cells more responsive to radiation, but instead of being eliminated completely, Koschmann and his team discovered that another checkpoint gene—Checkpoint Kinase 2 (Chk2)—"fills in" when Chk1 is silenced, enabling the mutated cells to survive the radiation to some degree.

With this knowledge, the team investigated radiation sensitizing ATM inhibitors.

"When we added ATM inhibitors to a standard course of radiation for mice with gliomas with mutated ATRX, we witnessed much longer survival rates—triple the survival rate than using only radiation therapy. We didn't see this in the glioma with non-mutated (wildtype) glioma. The ATM inhibitors basically turn off the only remaining checkpoint. The ATRX-mutated cells can't handle the damage," Koschmann says.

The team is investigating potential for a clinical trial testing ATM inhibitors.

Social factors tied to worse health outcomes in MENA community

HEALTH EQUITY ↔ A study from Rogel researchers looked at social factors that most concerned Middle Eastern and North American populations and how those issues impacted their health outcomes.

One-third of the 412 MENA adults surveyed listed transportation barriers to health care, one-third noted food insecurity and a quarter cited financial strain.

In adjusted models, people who said they were treated unfairly or were afraid of deportation had more social risk factors, which was in turn associated with more chronic conditions, more mental health symptoms and worse health overall.

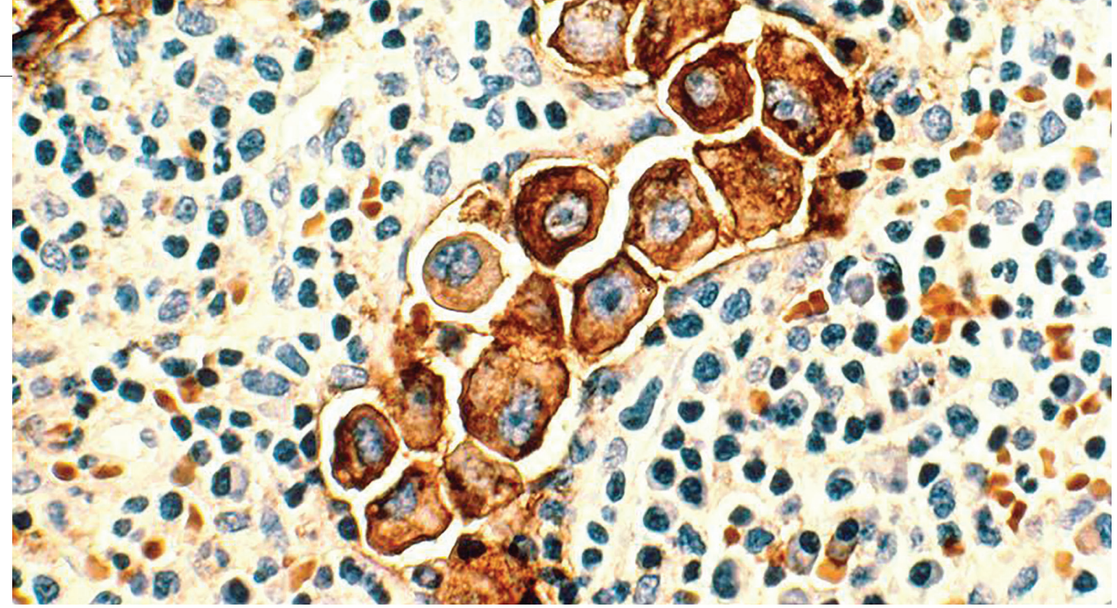
The study, led by **Minal Patel, Ph.D., M.P.H.**, and **Kenneth Resnicow, Ph.D.**, was published in the *Journal of Immigrant and Minority Health*. The findings suggest developing social needs screening and referral models that better serve the MENA community.

Michigan Public Health database serves as resource for researchers on Tobacco 21 laws

PREVENTION ↔ Researchers can now utilize a new interactive tool housing U.S. data on Tobacco 21 (T21) laws—regulations that raise the minimum age of the sale of tobacco products to 21. The Tobacco 21 Population Coverage Database documents T21 laws at local and county levels between 2014 and 2019, when T21 laws were rapidly growing across the country. Studies have shown that 85% of daily smokers begin smoking before age 21; thus, restricting the sale of tobacco products to individuals 21 and over can reduce overall tobacco usage.

Nancy Fleischer, Ph.D., M.P.H., who worked on the database, highlights that data collected for this tool can be used by researchers to further study the effects and public health impact of T21 policies. "We created this database to estimate the proportion of the U.S. population covered by T21 laws over time," she says. "Other researchers can now link these data to other data sources, as we did recently in a paper in *Preventive Medicine Reports* examining the impact of T21 laws on youth smoking initiation."

Photo: NCI — Visuals Online



Study finds nanomedicine targeting lymph nodes key to triple-negative breast cancer treatment

THERAPEUTICS ↔ In mice, Rogel researchers found that using nanomedicine to target lymph nodes and tumors simultaneously can remodel the immune microenvironment for long-term remission and lung tumor elimination in metastatic triple-negative breast cancer, or TNBC.

Study author **Duxin Sun, Ph.D.**, says that previously developed immunomodulators work well in animal models but fail in clinical trials. He and his team wanted to come up with a better approach that would treat TNBC patients long-term that could withstand the rigor of clinical trials.

"People don't pay enough attention to the lymph node microenvironment," Sun says. "But it's equally important. The lymph nodes play a crucial role in initiating the progression and metastasis of cancer."

Sun's team treated breast cancer mice models with an albumin nanoparticle, a type of nanomedicine, called Nano-PI, in combination with immunotherapies, to remodel the microenvironment in both lymph nodes and tumors. Nano-PI not only enhanced the delivery of immunomodulators to both lymph nodes and tumors, but also improved the drug accumulation in the macrophages of these two tissues. The study was published in *Science Translational Medicine*.

"What we found was striking," Sun says. "If we used this nanoparticle to deliver drugs to modulate the tumor and lymph nodes, we achieved long-term tumor remission and eliminated lung metastases, which we'd never seen before."

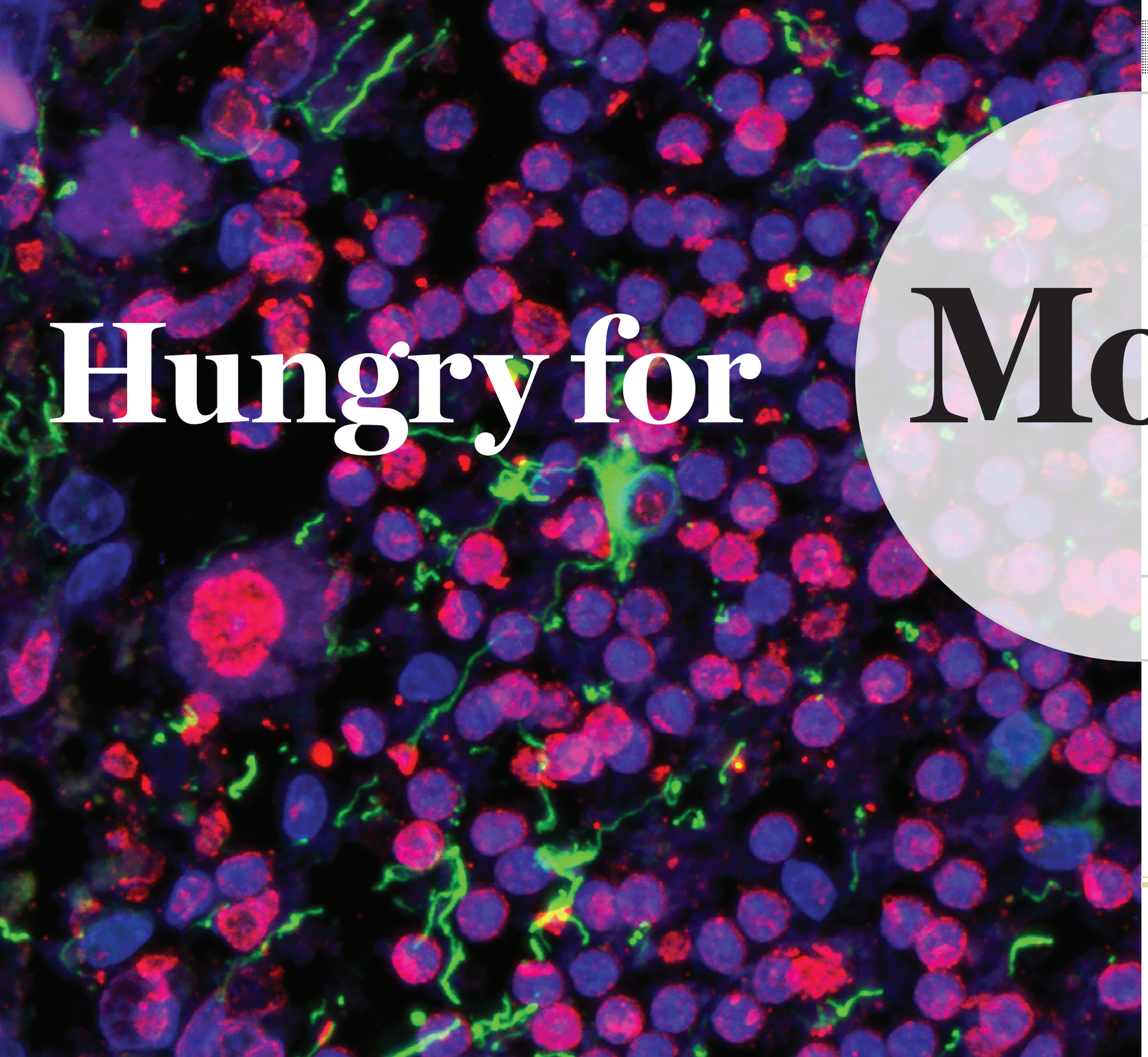
Skin cancers arise from a cascade of mutations

MOLECULAR DETERMINANTS ↔ The most common mutation seen in the most common type of skin cancer, basal cell carcinoma, isn't enough to trigger the disease completely. Instead, secondary mutations are necessary to rev up tumor growth, according to a study led by **Sunny Wong, Ph.D.**

Typically, basal cell carcinomas harbor many mutations. It starts with Ptch1, the loss of which activates the Hedgehog signaling pathway, resulting in early microscopic tumors. These tumors generally exist in a dormant state.

To identify which mutations in addition to Ptch1 are required to drive cancer progression and which are merely random passengers, the team then generated mouse models that allowed larger tumors to form alongside dormant microscopic lesions. They found that larger tumors acquired additional mutations that enabled them to escape and overcome dormancy. This can happen through a variety of mechanisms that further hyperactivate Hedgehog signaling, including amplifying Gli1/2 and upregulating Mycn. The findings are published in *Cell Reports*.

Photo: Emily Wyatt, Mark Davis



Hungry for More

Metabolism pathways make tumors sensitive or resistant to treatments. A collaborative group of Rogel researchers is leveraging these avenues to explore the growing foundation of new potential therapies.

By Anna Megdell

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etabolism is having a moment. Not a flash in the pan kind of moment, but one that highlights possible opportunities that might have otherwise stayed in the dark.

Advances in the lab like improved measurement of metabolism in tumors using PET scans, mass spectrometry and stable isotope tracing, the development of new and better drugs that can block metabolic pathways in cancer and a deeper understanding of the relationship between metabolism and the immune system all point to real hope that the time is now to target metabolism to improve cancer therapy, especially in those forms of cancer that don't respond well to current treatments.

At Rogel, a collaborative group of researchers have formed the Cancer and Immune Metabolism Working Group to unravel the nuances of metabolism across the spectrum of cancer research. But as program co-director **Costas Lyssiotis, Ph.D.**, notes, understanding just what metabolism means in this context, and the potential it holds for unlocking discoveries, takes a minute to process.

"The term metabolism is so wide-ranging," Lyssiotis, Maisel Research Professor of Oncology, says. "It is used by scientists and the lay public alike. The lay public uses it to refer to how quickly you're able to digest the apple you had at lunch. But scientists understand it as all of the biochemical reactions that occur in a system, be it a cell or a person, that allow that system to carry out a certain function. In cancer, that means turning nutrients into tumor cells."

"Scientists understand [metabolism] as all of the biochemical reactions that occur in a system, be it a cell or a person, that allow that system to carry out a certain function," says Costas Lyssiotis, Ph.D.

Lyssiotis's lab studies immune metabolism in pancreatic cancer. "We're trying to understand how the metabolic alterations in pancreatic cancer cells can prime them to be treated," he explains. The lab studies different metabolic pathways that pancreatic cancer cells use to grow and researches ways to target them. The team has described important roles for metabolites like the amino acids methionine and arginine, as well as non-traditional metabolites, to see how these nutrients fuel and sensitize cancer cells and the immune system.

Recently, they discovered that pancreatic cancer cells can grow by eating hyaluronic acid. The molecule is most well-known for its role in joint lubrication and skin tension as a supplement and beauty care product. But in this case, non-cancer cells in the tumor make hyaluronic acid, a phenomenon that is unrelated to supplements and joint health. The results, published in *eLife*, provide insight into the ways pancreatic cancer cells grow, which could indicate new possibilities to treat them.

And while the research is *not* implying that the presence of hyaluronic acid causes pancreatic cancer, their data illustrate that how pancreatic tumors make hyaluronic acid to feed the cancer cells could reveal new therapeutic targets.

"A central driving theme in my research lab is that pancreatic cancer doesn't respond to the common arsenal of treatment approaches. We need to think about this challenge differently, and we have taken the approach of defining and targeting the spectrum of nutrients from which cancer cells derive their energy," Lyssiotis says. "Then we use this information to design new, tumor-specific drug targets to starve cancer cells."

Collaboration and Context

One way of doing this is looking at how metabolism research intersects with other research disciplines, like immunotherapies, to create the right context for drugs to work more effectively. Lyssiotis's lab worked with **Marina Pasca di Magliano, Ph.D.**, Maude T. Lane Professor of Surgical Immunology, on an experiment in mice that showed how pancreatic tumors actively deplete the amino acid arginine. Blocking this metabolism did not slow tumor growth, but it did lead to more anti-tumor immune cells in the tumor. This prompted a test with immunotherapy. By blocking arginine metabolism together with immunotherapy, pancreatic tumor growth was considerably decreased.

Similarly, in a study with **Weiping Zou, M.D., Ph.D.**, director of the Center of Excellence for Cancer Immunology and Immunotherapy at Rogel, they found that an increase in the amount of methionine, another amino acid, promotes anti-tumor activity of the immune system. "You have competition between tumor cells and immune cells for methionine. If you starve the tumor cells of methionine, the immune cells don't get it either. You want to selectively delete the methionine for the tumor cells and not for the immune cells," Zou says.

"Just changing methionine alone would do nothing," Lyssiotis adds. "But the increased amount of methionine creates the right context for immune therapies to work better."

Lyssiotis collaborates with program co-director **Daniel Wahl, M.D., Ph.D.**, associate professor of radiation oncology, as part of the Cancer and Immune Metabolism Working Group. Wahl's work focuses on making an impact for patients with glioblastoma. "In the lab, we found that certain metabolites called purines cause brain tumors to be resistant to standard treatments. Once we knew this, we knew we needed to figure out how to measure purine metabolism in brain tumors, something no one has done before," he says. That work originated in the lab, but Wahl and his team have now measured this metabolic pathway in about 10 patients with brain tumors. "Once we saw that blocking this pathway made treatment work better in mice, we knew we had to get it to the clinic."

Wahl worked with a team that included co-principal investigator and clinical assistant professor of neurology **Yoshie Umemura, M.D.**, to write, fund and open a clinical trial where a purine inhibitor is combined with standard brain tumor treatments. The trial is about halfway complete, and Wahl is optimistic about the results. "Along the way, the frequent input and collaboration from members of the Cancer and Immune Metabolism Working Group have been critical for getting this work done," he says.

Partnerships formed in the working group have led researchers to new possibilities in the treatment of childhood brain cancer as well. **Sriram Venneti, M.D., Ph.D.**, associate professor of pathology and scientific research director of the Chad Carr Pediatric Brain Tumor Center, is also a co-director of the program. The Venneti lab researches the core mechanisms that drive diffuse intrinsic pontine gliomas, or DIPG, and ependymomas in children.

They do this by examining the relationship between metabolism and epigenetics. As Venneti explains, the main drivers of childhood brain cancer are epigenetic: changes in the way DNA is "read" rather than changes to the DNA itself. Recent work has shown that metabolism is a primary regulator of epigenetics. "When looking to see how metabolism drives the growth of childhood brain tumors, we need to understand the link between epigenetics and metabolism because there's crosstalk between them," he says. "Epigenetics says something to metabolism, and metabolism says something back to epigenetics. They're constantly talking to each other to keep the cancer growing."

Photo: Leisa Thompson

Photo: Leisa Thompson

When targeting metabolism, the idea is to find the metabolic pathways that fuel cancer cell growth and stop them. Venneti says that these metabolic endpoints act as gas or brake pedals to access the other elements that drive the tumor. "Cancer cells feed a lot because they're continuously dividing," he says. "If you inhibit these feeding mechanisms, then you can cause the cells to die. We're using this strategy to prevent energy production in cells, but at the same time we're also suppressing epigenetics by using the same targets. That's the goal."

In one study, Venneti's lab found an unexpected result in childhood ependymoma: repurposing metformin, a drug used to manage diabetes, was helpful when looking at animal models of ependymoma. Metformin not only suppressed mitochondrial metabolism, but also changed the epigenetics, which has implications for disease recurrence. The ability to target metabolic and epigenetic endpoints at the same time speaks to the importance of the immune system in this research.

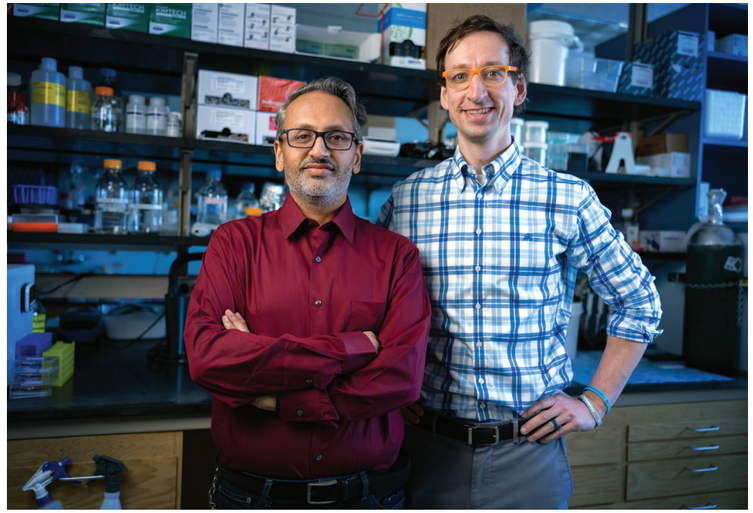
"Playing with metabolic pathways is important because you have immune cells in the tumor microenvironment, apart from the tumor cells, that react in different ways to different metabolites, or they produce different metabolites," Venneti says. "Some therapies can kill tumor cells but simultaneously activate the immune system. There is a dual advantage as we look to the future and immunotherapies become more prevalent."

Where We've Been, Where We're Going

For the working group, understanding cancer metabolism to identify new drug targets lies at the heart of their research. However, cancer cells are highly adaptable and readily evade metabolism-directed strategies. Thus, an area of active research lies in understanding how cancer cells adapt.

For **Deepak Nagrath, Ph.D.**, associate professor of biomedical engineering, targeting metabolism allows researchers to crack open that foundation of the cancer cells, inhibiting them from rewiring the microenvironment. "In our lab, the thought process has been that cancer cells cannot die because they're more focused on scavenging things from the microenvironment so they can grow," he explains.

Nagrath is a biomedical engineer, and his lab looks at how the tumor microenvironment communicates with and fuels these cancer cells. "We've seen that the microenvironment can supply nutrients like amino acids to cancer cells. We've also shown that the microenvironment supplies vesicles, which are loaded with nutrients that the cancer cells engulf to use for their own growth."



For the Cancer and Immune Metabolism Working Group, collaboration is key to finding new ways to leverage metabolic pathways to improve treatment for patients. Pictured above: Yoshie Umemura, M.D., and Daniel Wahl, M.D., Ph.D. (top); Sriram Venneti, M.D., Ph.D., and Carl Koschmann, M.D.

Photos: Erica Reist Bass, Bryan McCullough

Like the other members of the working group, Nagrath is hopeful that understanding metabolism in the lab will eventually lead to new treatment options, given that, as he describes, most conventional therapies have failed to meet the mark. "In some cancers, like pancreatic and ovarian, we've been using the same drugs for 40-50 years. There aren't many new therapies," he says. "And these have failed because cancer cells adapt and come up with ways to compensate."

But to accomplish this, Nagrath says that a complete and dynamic understanding of the metabolic environment is necessary to truly starve the cancer and incapacitate its growth.

"That's why the metabolic goal is systemic. It systematically starves cancer cells, so there's no way for them to get around it," he continues.

For metabolic treatments to have a clinical impact, Nagrath's lab focuses on a two-pronged approach. Using patient genomic data in integrated machine learning, along with a state-of-the-art metabolic flux analysis framework, the lab has identified backup metabolic genes, or collateral genes, on which cancer cells rely for their growth. They're also developing a novel platform for predicting in vivo metabolic fluxes in patients, which will be a cornerstone for targeting therapy.

When thinking about the future of metabolic research, Lyssiotis has his eye on diet and cancer, a realm that he says for-profit companies and false marketing exploit, despite zero evidence that changing diet alone meaningfully affects cancer growth.

Still, Lyssiotis says that understanding the principles of metabolism, and how cancer cells feed, can create a context for diet to act as medicine. For **Yatrik Shah, Ph.D.**, this means researching to see if dietary changes or probiotics can enhance the anticancer metabolites, or alter microbial gases, generated in the microbiome. His lab focuses on the intersection of metabolism, microbes and diet in colon cancer. As he explains, the microbiome is a dense community of bacteria mostly localized to the colon that generates thousands of unique metabolites and dozens of biologically active gases, all of which are dynamically changed by the diet.

"In the lab, we found microbial metabolites can alter cancer metabolism and impact cell growth and treatment response," says Shah, Horace W. Davenport Collegiate Professor of Physiology. "We identified several metabolites generated by microbes that enhance cancer growth by providing key nutrients. We also found microbial metabolites that selectively kill cancer cells by altering and inhibiting key metabolic steps in cancer."

"Playing with metabolic pathways is important because you have immune cells in the tumor microenvironment, apart from the tumor cells, that react in different ways to different metabolites, or they produce different metabolites."

Sriram Venneti, M.D., Ph.D.

Lyssiotis uses the popular ketogenic diet as another example. Recent studies have shown that, like people, animals on a ketogenic diet have lower glucose and insulin. And in the context of low glucose and low insulin, tumors are now more susceptible to certain drugs.

"If you recognize what the ketogenic diet does to the body, then you can harness that information to make drugs more effective," he says. "We know that immunotherapy sometimes works great, and sometimes it doesn't. But if you can make it work in an area where it's not currently working, like in pancreatic cancer, by influencing diet, then it's going to change the paradigm.

"I'm not saying that changing diet automatically changes the disease," Lyssiotis continues. "There's still work to be done there. But it's about using the principles and a molecular understanding of metabolism to improve drug effectiveness."

Hitting the Mark

Circulating biomarkers, a new frontier in cancer care, bring both hope and unease to the clinic. Rogel researchers are unraveling their nuances, advancing enabling technologies, advocating for patients and figuring out how to ethically integrate this technology into clinical care.

By Anna Megdell

Illustration by Alex Webber

Imagine a patient comes in for a routine check-up, no symptoms or signs of anything wrong. A blood test reveals markers of early-stage cancer, one that can be cured by surgery.

For a patient receiving chemotherapy, the same type of blood test suggests the cancer is shrinking. In another patient, it points to signs of cancer progressing.

Or, a patient has been told the cancer is removed and they are doing well, but a blood test suggests it's coming back.

What do the results mean in each situation? How does it influence the next step?

So-called liquid biopsies or circulating biomarkers are a promising beacon for diagnosing cancer or detecting early signs of treatment resistance or metastasis. But researchers' opinions differ about the effectiveness of the nascent technology—how, and in what settings, can they actually benefit patients?

Circulating tumor biomarkers, found in body fluids such as blood, are proteins, DNA or other substances released by cancer cells, or even cancer cells themselves. These substances or cells come from the cancer tissue and are not seen in normal cells. For solid tumors, the potential of liquid biopsies offers researchers a possible additional tool in their toolbox for measuring treatment response, especially when tumor tissue can't be easily reached by imaging or standard biopsies.

Traditionally, researchers track tumor shrinkage or growth by measuring the size of the cancer through physical examinations or radiology tests. But what if looking at circulating biomarkers first could tell researchers about the tumor's responsiveness? If the tumor is growing, researchers might detect more tumor biomarkers in the blood. And if the tumor is shrinking, those same levels may decrease or become undetectable.

Use of circulating tumor markers to track cancer in patients with established metastases, or even in patients who have had cancer in the past and are being monitored, is a well-accepted clinical strategy for many different kinds of malignancies. However, using liquid biopsies to detect a new cancer in a subject without a cancer diagnosis is far from proven. Several recent preliminary

In his research, Muneesh Tewari, M.D., Ph.D., has explored the whole spectrum of circulating biomarkers. "There's always a tension between something new that looks promising and the extent to which you jump forward and start using it, versus validating it and making sure the data is believable," he says. "We need both viewpoints."

Photo: Joseph Xu, U-M College of Engineering

studies have suggested that when a blood test demonstrates circulating DNA harboring one or more mutations, it signifies a cancer is lurking in that person. Since these mutations might come from many different cancers, they have been called multiple cancer early detection, or MCED, tests.

While a lot of hope surrounds this burgeoning methodology of MCED tests, **Daniel Hayes, M.D.**, Stuart B. Padnos Professor of Breast Cancer Research at Rogel, urges colleagues to be honest about the current state of the research.

"Right now, though many researchers and clinical trials are studying it, there aren't any liquid biopsies proven not just to identify the possibility that the person has cancer, but also to demonstrate that this knowledge helps treat them better," he says. "We're just not there yet."

With this reality, Rogel researchers work to move this promising research forward and clarify this complexity in the clinic.

The Earlier the Better

One element of circulating biomarkers that researchers do agree on is in the space of treatment response. Studies indicate that tracking these tumor markers could provide additional data to help determine if therapy is working much sooner than traditional forms of tracking, like CT scans or MRIs.

In a phase 1 clinical trial, **Carl Koschmann, M.D.**, pediatric neuro-oncologist at the University of Michigan Health C.S. Mott Children's Hospital and clinical research director for the Chad Carr Pediatric Brain Tumor Center, examined cerebrospinal fluid and plasma from patients with diffuse midline gliomas over many months, collecting hundreds of samples through blood draws and lumbar punctures across multiple sites. Koschmann and his team were tracking changes in cell-free tumor DNA (the DNA that circulates in blood and plasma) as glioma patients received treatment concurrent with the clinical trial. Would the cerebrospinal fluid and blood draws hold clues to how the patients were responding to treatment?

The study revealed some promising results. Tumors grew more slowly or took longer to recur in those patients whose allele fraction—the amount of mutant DNA—decreased after receiving the clinical trial drug. This tracked with the researchers' initial expectations.

But the CSF also revealed something that couldn't be found in MRI imaging alone: researchers saw a spike in the amount of mutant DNA *before* the tumor's growth was captured on the MRI. This was the first study of its kind to collect serial CSF in a clinical trial for gliomas.

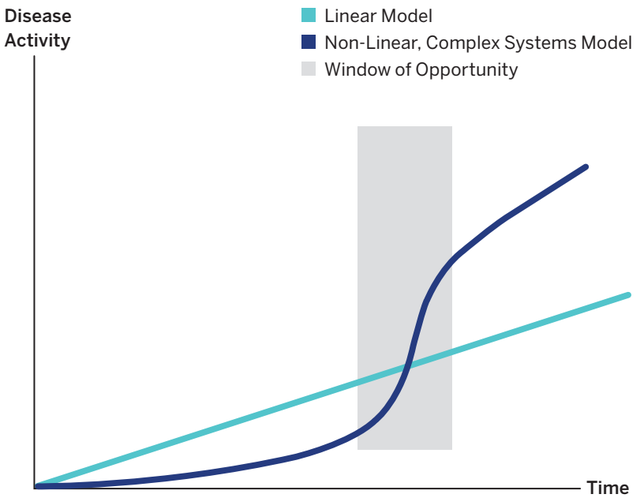
"It is very clear that DNA in the CSF can provide a lot of new information about the state of the tumor," Koschmann says.

Liquid biopsy presents an especially good opportunity for cancers like glioma, where it's difficult to measure tumor growth and obtaining a traditional tissue biopsy is not feasible.

"If a patient were to come into the clinic right now with a high-grade brain tumor, we'd take an MRI and then make inferences from that imaging about how things are going. But there's a lot of handwaving about what it means, because it's the only piece of data we have about how things are going," Koschmann says. "Patients don't want to wait until the MRI worsens to change course. Having early information that you might need to adjust treatment is very valuable."

Finding the window

Muneesh Tewari, M.D., Ph.D., explains: "The linear model of the creation of disease means that cancer would grow steadily, and biomarkers released into the blood would likewise increase steadily over time in the blood. The non-linear model, which we hypothesize is more accurate, indicates that there is a phase in which cancer growth and the amount of biomarker detectable in the blood rises sharply, even before symptoms develop and while the cancer is more easily curable. It is that phase, which we see as the 'window of opportunity' to detect and treat cancer early, that we aim to make visible through liquid biopsy-based testing."



We Need Both

Sunitha Nagrath, Ph.D., professor of chemical and biomedical engineering, works to develop methods that can isolate, analyze and enable implementation of blood-based biomarkers in the clinic. She says this technology holds tremendous opportunities to monitor patients non-invasively, and to underpin the ever-changing molecular phenotypes of a tumor in response to treatment.

"Blood-based biomarkers have changed the landscape of precision medicine. Blood has such a wealth of information, and even with a century of drawing blood routinely for basic patient care in modern medicine, we've only scratched the surface. Blood has so much more to offer," she says.

Muneesh Tewari, M.D., Ph.D., agrees that the research surrounding circulating biomarkers, and the speed with which this area has progressed, holds tremendous hope for the future of clinical cancer care.

Tewari, Ray and Ruth Anderson-Laurence Sprague Memorial Research Professor, uses next generation sequencing and computational biology techniques to develop biomarker approaches for cancer early detection, disease monitoring and treatment response prediction. A professor of internal medicine and biomedical engineering, Tewari's lab discovered that in addition to circulating cell-free DNA, RNA could also be found in the bloodstream as a circulating marker, which hadn't been previously studied extensively.

"Nobody really expected to find them," Tewari says. "This basic science perspective started my own journey in the field, trying to figure out why circulating RNA biomarkers are there, what cells they are coming from and how they get into the bloodstream."

When he moved to U-M in 2014, Tewari started studying cell-free tumor DNA in addition to RNA in the blood. He and his team have explored the whole spectrum of circulating biomarkers, from his basic science foundation to translational work and now into improving the technology and application.

Broad collaboration is characteristic of this work, given the new and malleable nature of the research. Tewari works closely with head and neck cancer researchers **J. Chad Brenner, Ph.D.**, and **Paul Swiecicki, M.D.**, to develop better assays in the blood to test biomarkers more effectively. The team has also been developing tools and technology and gathering clinical data to measure cell-free tumor DNA in urine samples as a surrogate for blood samples.

"We're testing to see whether these blood tests could be converted to urine-based approaches, because urine is completely noninvasive," Tewari explains.

The idea is that some of the tumor DNA in the blood gets broken down and passes through the kidney's glomerular barrier. Normally, this barrier prevents large molecules in the blood from getting into the urine, but small fragments of DNA actually do get through.

As someone who has studied circulating biomarkers for over a decade across the spectrum of care, Tewari says that continuing to improve existing tests, developing new tests and investing research into new methodologies is vital because of its profound significance for patients when it comes to early intervention, treatment and recurrence response. Further, the mutations in circulating cell-free DNA may not only reveal that something is going on but also provide insights into

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Carl Koschmann, M.D.

specific therapies that might target the mutations found in the DNA.

"Fifteen years ago, if somebody with metastatic disease wanted to find out what mutations were present and we didn't have access to enough primary tissue—something that's very common in lung cancer, for example—we would have had to do an invasive biopsy," Tewari says.

Today, he notes, while many patients with metastatic cancer need a biopsy to diagnose the disease, a blood sample can determine which mutations are present and how they're changing.

"It's a big deal," he says. "When we started using the term liquid biopsy in 2006, it was a dream. Now it's clinical practice from some indications, with many applications on the horizon that are being investigated: early detection of recurrence, monitoring treatment response and ultimately early detection of primary cancer. Each is a huge opportunity for changing patients' experience and outcomes."

Despite this hopefulness, Tewari understands the concerns some have around just how new this technology is. He understands it as an inherent part of the process of any kind of medical advancement.

"Of course, there are many issues that need to be ironed out and processes that need to be regulated," he says. "But there's always a tension between something new that looks promising and the extent to which you jump forward and start using it, versus validating it and making sure the data is believable. We need both viewpoints. We need to make sure everything is rigorously developed and thoroughly vetted, without which we would have a big mess. At the same time, if we didn't have some pressure to move things forward and get them into application, it could take decades of just refining and refining, which could be a missed opportunity to benefit patients."

This is the moment researchers find themselves in: a space where data look promising, and because of commercial pressures, people want to jump ahead. And patients want answers. At the same time, researchers and research-minded physicians understand the necessity to ensure that what is actually being offered to patients is reliable and adds value for patients without causing harm.

"The tension is getting worked through," Tewari says. "Sometimes it can take years. But eventually, like with any creative process, which research certainly is, that tension will hopefully make the outcome better for patients."

Part of the Tension

The fulcrum of this issue with the most urgency—in both the potential to improve clinical treatment options and in the wariness of the nascent technology—hinges on its implications for patients and the patient experience.

Some researchers argue that incorporating liquid biopsies into care now is worthwhile given the quicker turnaround of test results for patients. "If someone can know sooner that their tumor has a particular mutation that can be treated with a particular targeted therapy, it can relieve unnecessary stress and anxiety," Tewari says.

But aside from its ability to track disease progression and recurrence, circulating biomarkers have been touted by companies as a way to detect cancer in otherwise healthy folks, which researchers agree is a breeding ground for unnecessary anxiety for patients.

One of the biggest dangers is false positives, says **Elena Stoffel, M.D., M.P.H.**, clinical associate professor of gastroenterology, who focuses on early detection and cancer prevention.

"All of us have circulating cells that are not normal. Your body's immune system is in charge of getting rid of cells that are not normal, that are going off program. As we get older, the proportion of cells that are not normal goes up as a normal function of aging. We develop more abnormal cells and many of those abnormal cells may never develop into a cancer, but they may be detectable through some of these biomarker tests," she says.

The issue lies in the sophistication of liquid biopsy tests used to detect cancer in otherwise healthy patients without symptoms.

"We don't know what the burden of cells has to be to make one of these liquid biopsy tests positive. We don't know what the sensitivity or specificity is for these tests. Therefore, it's possible that entirely by chance, one of the samples might have markers of just a small number of cells that are not normal," Stoffel says.

The worry is: What do you do when you find that? Where are the cells coming from? What type of cells are they? And if we can tell what type of cells are abnormal, what do we do about that? Do we then go on a diagnostic odyssey involving invasive tests?

"We end up chasing what might be a red herring," Stoffel says.

Stoffel, who directs Rogel's Cancer Genetics Clinic, works closely with patients who have greater risk of developing cancer because of genetic mutations that run in their families. For this population, the conversation of circulating biomarkers and liquid biopsies gets even trickier.

Elena Stoffel, M.D., M.P.H., directs Rogel's Cancer Genetics Clinic. "I think about a test and the clinical utility of a test by asking, 'What would I do differently with this information?' Because if their imaging is negative and the biomarker test is positive, what are we going to do?"

"For families at-risk of, say, pancreatic cancer, the recurrent pancreatic cancer screening recommendations are imaging of the pancreas with endoscopic ultrasound or MRI of the pancreas," she explains. "But there is a biomarker test for pancreatic cancer risk on the market. It's not FDA-approved, but it's on the market. I've had several patients ask, 'Well, should I be doing this in addition to my imaging?'"

Stoffel's answer? "How is this information going to change anything?"

"I think about a test and the clinical utility of a test by asking, 'What would I do differently with this information?'" she says. "Because if their imaging is negative and the biomarker test is positive, what are we going to do? Will that information keep the patient up at night? And if the imaging is negative, there isn't really anything that we can do if the blood test is positive, other than watch and wait—which is what we're doing anyway with the imaging alone."

"Another possibility is that the blood test is positive and cancer is found, but maybe that cancer was never going to be clinically evident," Hayes adds. "In this case, if we do something, is it the right thing for the patient? Given the potential harms of surgery, radiation and systemic therapies for cancers, we need to be sure that a strategy focused on early detection by a liquid biopsy improves a patient's survival compared to not doing the liquid biopsies."

When it comes to cancer screening and prevention, Stoffel says it's important to look to the tests that have proven benefit.

"We know that colon cancer screening and breast cancer screening have proven benefit. But currently, we don't have any data that shows proven benefit to using a blood-based biomarker test or circulating tumor cells in healthy patients," she says.

Another concern for Stoffel and Hayes is the risk of false negative tests for those cancers with proven screening methods, like mammography for breast cancer, Pap smears for cervical cancer, colonoscopy for colorectal cancer, high resolution CT scans for lung cancer and more.

"If an MCED test is negative, will patients assume that they don't need to have these standard screening tests performed?" Hayes says. "We already have evidence that current MCED tests are not always positive when the standard screening tests do show something. It would be terribly unfortunate if the blood MCED tests start to give people a false sense of security. Clearly, nobody likes to have a colonoscopy, but people should not use a negative blood test to forego this life-saving technology.

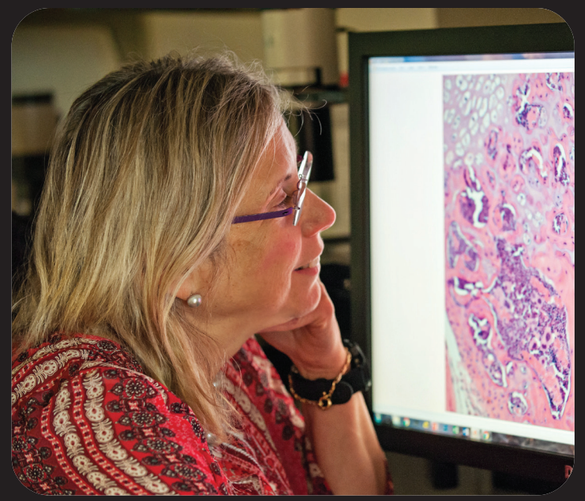
"We're just not there yet."

In addition to not being FDA-approved, many of the tests on the market that claim to identify disease in otherwise healthy people will require years' worth of big trials to truly test efficacy, and undertaking those trials, Hayes says, "will require tens, or even hundreds, of thousands of participants and long-term follow-up, which will consume a lot of resources and cost a lot of money."

For Tewari, optimism about this technology's ability to detect cancer progression lies in keeping a wide lens.

"Fifteen years ago, any application of these new types of circulating biomarkers was a dream. Today we have tests that are useful at determining what mutations a patient's cancer has, and ones on the horizon to track recurrence," he says. "I look at it from that perspective. We just have to manage that tension and do this right—don't jump forward too quickly but nor should we resist advancement. We need to create and use tests that don't cause harm and that deliver actual value.

"But in the big picture, I feel like the field is on a good track."



Problem Solvers

When the pandemic hit, Rogel researchers, clinicians and staff needed to rethink how they did their work. In doing so, they discovered new ways to fulfill the cancer center's mission despite unprecedented uncertainty.

By Mary Clare Fischer
Photographs by Leisa Thompson and Erica Reist Bass

In mid-March 2020, the orders came to shut everything down.

With COVID-19 rampaging throughout the world, researchers across the University of Michigan were forced to power off their labs. New enrollment in clinical trials paused. In-person clinics were canceled unless there was an emergency.

The health care workers and scientists at the Rogel Cancer Center immediately understood the need for these restrictions. And as time wore on, it became clear that these disruptions were not going to be short lived.

"We thought at first we would be out for maybe two weeks, that we would send everybody home and regroup," says **Mathew Innes**, director of the Oncology Clinical Trials Support Unit at Rogel. "Then we just kept staying and staying and staying."

But as the pandemic continued to evolve, the work never really stopped. Rogel staff and faculty members needed to figure out ways to innovate their research, collaborate to meet patient needs and be efficient despite the uncertainty swirling around them.

Here's what they did.

'Just Revolutionary'

When the order came to restrict in-person clinic visits, emails were flying with ideas about what to do.

Sofia Merajver, M.D., Ph.D., director of the Breast and Ovarian Cancer Risk Evaluation Program at Rogel, remembers turning to her team of three genetic counselors and one scheduler. "I felt a certain sense of going to battle," she says. "There was a problem in front of us, and we had to meet it."

She told her team, "We are going to have a full clinic on Monday. We're going to see everyone by telephone or video. We'll document everything we do the usual way and worry about who pays for what later. We won't cancel a single patient."

And they didn't.

"I'm a researcher, so I suppose you could define me as somebody who lives by her wits," Merajver says. "There was this idea of bringing forth our problem-solving ability, which is how we make a living as scientists, right?"

To pull this off, Merajver's team organized what she calls a clinical conference. Her genetic counselors created a PowerPoint that featured a "nutshell of information" about every patient the team would see the following Monday.

Each Friday, they'd go over the presentation and over the weekend, Merajver would memorize the details of anywhere between 17 and 20 patients.

Merajver says she's always tried to learn everything she can about a patient before their appointment, as she was taught during her training at the University of Michigan Medical School. But committing more than a dozen patient biographies to memory at one time was a new test for her recall.

"I'm not an actress, you know," Merajver says. "I'm not used to memorizing the whole of *Macbeth*. But I challenged myself to learn a radically new way of getting to know patients."

On Mondays, Merajver and her team would see new patients by phone or video every half hour from 8 a.m. to 4 p.m., without any breaks to go to the staff room and debrief.

Despite this pace, Merajver says, her team found they often did a better job serving patients with telehealth.

"Seeing patients faster, seeing relatives of patients that we are certain have a gene mutation, seeing a lot more patients from remote locations, a lot of patients who are transportation-challenged—it's been just revolutionary for us.

Sofia Merajver, M.D., Ph.D., and her colleagues reorganized how they work to continue to see patients virtually. "I felt a certain sense of going to battle," she says. (The above photo was taken before the COVID-19 pandemic.)

"And you know what?" she continues. "The way we did it at the beginning, with this conference, is the way we still do it now. Three years later, we are doing exactly the same thing."

Exploring the Data

As the pandemic unfolded, **Goutham Narla, M.D., Ph.D.**, and his team were glued to the news.

The restrictions issued on biomedical research meant that Narla, a Rogel researcher studying how to activate faulty tumor suppressor proteins, needed to limit most of his lab's activities immediately.

All the cell-based assays stopped. Narla and his graduate students and postdocs froze the unique cell lines they'd generated. Fortunately, there weren't any ongoing animal studies that required multiple dosings, but the team had to go into emergency colony maintenance to keep their transgenic strains alive and well.

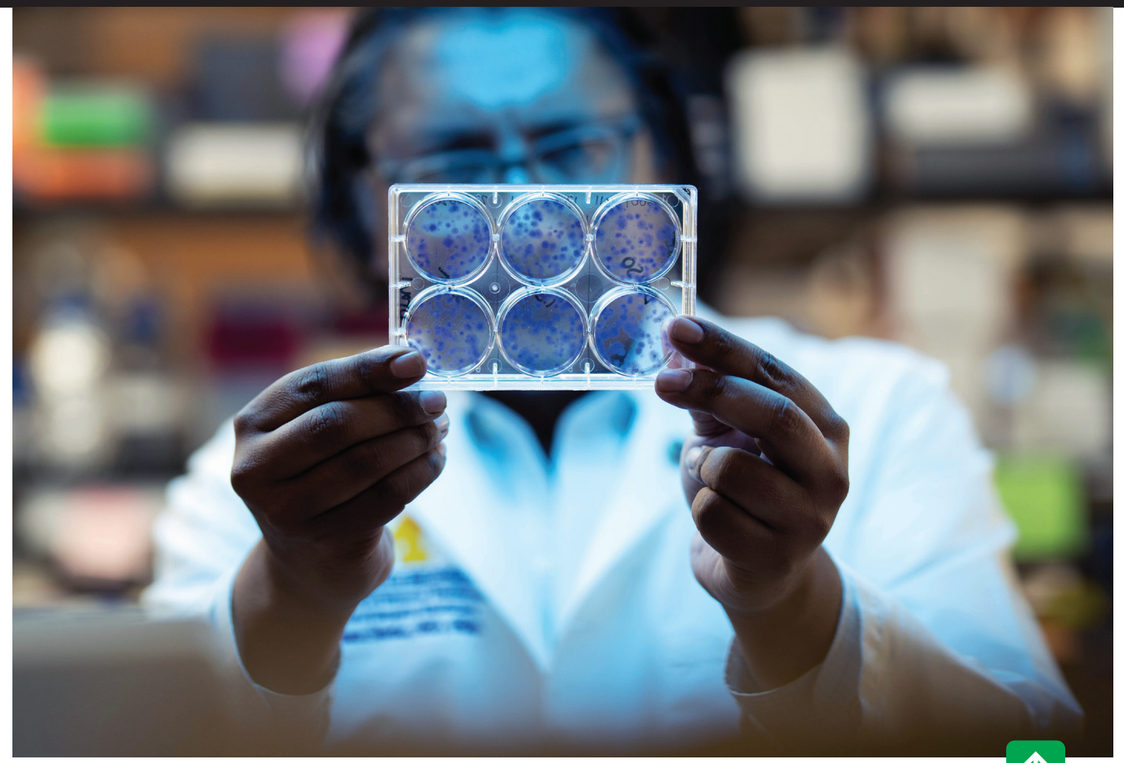
"At first, it was a major adjustment," Narla says. "We went from going at 100 miles per hour to zero."

Suddenly, Narla and his team found they had a lot more time on their hands. Amid virtual journal clubs and happy hours, they began thinking about what normally would fall to the bottom of their to-do lists, like reading more research literature and revisiting old data that could now be analyzed in new ways.

Once the team started digging into the past, they found possibilities for the future. For instance, a series of mutations in the amino acid Narla studied turned out to be different than what they'd originally categorized. These different mutations occurred in very specific tumor types, so the team hypothesized that they would point to different tumor biology, which has turned out to be the case.

Plus, they discovered that some small molecules they thought were inactive actually turned the tumor suppressor target off. These structurally similar molecules could allow them to confirm whether the drugs they would develop were specific enough.

"When you're screening thousands of molecules, sometimes you don't stop and assess the whole landscape," Narla says. "We're really able to do that now. With all of



> **“Over the course of many years, we’ve developed our ability to work through these challenges—not anticipating COVID, obviously, but anticipating the need to deal with this issue during crisis.”**
>
> Andrew Shuman, M.D.

that information, we have a lead molecule that’s about a year away from clinical trials and drug development for the first time.”

Training for Triage

Andrew Shuman, M.D., had been planning for this type of crisis for a long time.

The associate professor of otolaryngology and Rogel member is also an internationally recognized bioethicist, dealing in philosophical questions about when, how and in what order to provide health care and facilitate biomedical research.

“Especially in the world of cancer, where many of these health issues are urgent but not necessarily emergent,” Shuman says, “it’s quite complicated to think about how we can equitably and fairly, but also responsively, triage many aspects of care in a way that’s informed by good data and sound ethics and practice.”

As the co-chair of the Scarce Resources Allocation Committee at Michigan Medicine, Shuman was thrust into the spotlight at the beginning of the pandemic as he sought to create a framework that guided his peers in deciding which of their patients, including those who were immunocompromised, still needed treatment during a high-risk period.

Luckily, he’d been trained in an environment with a long history of crisis triage expertise. Bioethicists from the University of Michigan had developed an outline for how to allocate ventilators during the swine flu pandemic of 2009 and 2010, which the Michigan Department of Community Health then adopted as part of its plan for distributing scarce medical resources and services during public health emergencies.

“U-M has been active in this research, advocacy and policy space for decades,” Shuman says. “Over the course of many years, we’ve developed our ability to work through these challenges—not anticipating COVID, obviously, but anticipating the need to deal with this issue during crisis.”

“At first, it was a major adjustment,” says Goutham Narla, M.D., Ph.D., when his lab transitioned their work to virtual at the onset of the pandemic. “We went from going at 100 miles per hour to zero.”

When Shuman and co-chairs, **Marie Lozon, M.D.**, and **Sandro Cinti, M.D.**, had to ramp up their scarce resource allocation strategy during the current pandemic, they created specific working groups to deal with issues ranging from limited ventilators, dialysis machines and ECMO circuits to how to coordinate cancer care.

Shuman and others shared that expertise outside of University of Michigan’s campus as well, partnering with 28 other head and neck surgeons from different health care systems to create a novel cancer-specific tool to help prioritize surgical cases in the COVID-19 era. Their paper about development and validation of the tool was published in the journal *Cancer* in August 2020.

“I’m very proud of the efforts we put forward,” Shuman says. “Being prepared and proactive is one of the things we excel at as an institution.”

Virtual Community

By the beginning of 2022, Rogel’s Patient and Family Support Services team—a group of art and music therapists, social workers, chaplains and child-life specialists—had figured out how to meet patients where they were. They moved many of their offerings online and were hearing—and seeing—the benefits.

Missed appointments dried up. Patients who lived further away suddenly had more options to attend programs. They were more relaxed because they didn’t have to deal with the mental and physical exhaustion of 14 other appointments—and even if they were feeling awful, they could put up an avatar on their Zoom and still participate.

Noting how virtual programming allowed patients to show up more, and more easily—and that patients often loved it—the PFSS team created a new men’s support group.

On the second and fourth Mondays of the month, men being treated at Rogel can log into Zoom. **Bruce Paul**, one of the cancer center’s chaplains, starts by reading a virtue—things like *understanding* or *dignity*—and **Bob Huffman**, the music therapist at Rogel, plays

calming music. The ground rules: confidentiality, respect, letting everyone speak so no one monopolizes time.

The virtual format created a sense of community for men ranging from their early 20s to mid-60s who lived hours apart. The only denominator that mattered was cancer.

"Once it got rolling, the candidness and the comfort level was great," Huffman says.

The group discussed different topics like resiliency and legacy. They shared their fears of running out of treatment options and how lonely they often felt. People with cancers in male parts (prostate, testicle) mentioned the side effects from surgeries that had led to incontinence or intimacy issues.

"I don't think these guys would have come into an office or a room to do this," Paul says. "One of the blessings I've found from the pandemic is that we started these new technologies out of necessity, but we've kept it going."

'We Can Co This'

The word spread on social media about a group forming, a consortium of cancer centers that would band together to share data and best practices around COVID-19 and how it affected their high-risk patients.

Christopher Friese, Ph.D., R.N., Rogel's associate director for cancer control and population sciences, heard about the group from a researcher at Vanderbilt-Ingram Cancer Center who had built a registry to detail how cancer patients responded to COVID-19 and was looking to include as many institutions as possible.

Friese felt Rogel could add value to this community—if they got the right people involved. His own background in health services and quality would be helpful, but he needed a medical oncologist on board, too.

Leslie Fecher, M.D., professor of hematology/oncology and dermatology, had already reached out to **Anne Schott, M.D.**, the associate director for clinical research at the cancer center, about studying the experience of patients at Rogel with COVID-19.

Fecher and Friese partnered with Rogel's cancer registry, which has been collecting data on patients with cancer diagnosed or treated at Rogel since 1995. Together, they asked the institutional review board to accelerate the approval process for using this type of data.

"It really was a team approach," Friese says. "We involved a lot of partnerships to make this happen relatively quickly and nimbly."

The same could be said for the COVID-19 & Cancer Consortium as a whole. Just seven months after the consortium formed, it published a paper using data the group had gathered—an unprecedented turnaround in the research space.

More than 10 additional papers have come out of the consortium since, appearing in prestigious journals including *The Lancet*, *Cancer Cell* and various *JAMA* publications, and covering a range of crucial topics such as geriatric risk factors for serious COVID-19 outcomes among older adults with cancer, and racial disparities and regional variability in COVID-19 outcomes among patients with cancer.

"It shows you that with a little bit of elbow grease, people thinking creatively and this sense of urgency, we are able to break through a lot of the traditional barriers," Friese says.

"We can already see there's great potential for this beyond COVID-19. It's catalyzed a new approach of rapid cycle research. Now that we've developed the platforms, we know we can do this."

Continuing Trials

In the Oncology Clinical Trials Support Unit (O-CTSU), all didn't stop at the start of the pandemic.

Although the unit paused enrollments for new clinical trials during the first four months of the pandemic, existing trials with a potential therapeutic benefit kept going. But the group needed to figure out how to make the trial logistics possible when their on-site presence was extremely limited.

Like so much else during the pandemic, the answer lay with pivoting to virtual, creating consent forms that could be signed online and conducting study visits remotely when possible.

"Most patients were doing virtual visits. Very few were coming in person," says **Sujata Guduri**, administrative manager for the O-CTSU's clinic research group operations.

Yet one crucial element of clinical trials was a lot more complicated to do asynchronously: getting drugs to patients.

Michigan Medicine's research pharmacy already had some experience shipping medications on a limited basis, but now they needed to scale up—and cut through all kinds of red tape.

If a study medication was considered an investigational new drug, federal laws allowed for it to be shipped across state lines without restriction. Otherwise, Michigan Medicine needed to be cognizant of mail order pharmacy regulations regarding shipping to other states. Plus, the pharmacy needed permission from the study's principal investigator and the study sponsor.

Bruce Paul and Bob Huffman lead a cancer support group for men ranging from their early 20s to mid-60s. The virtual format enabled them to connect group members who lived hours apart.

If everyone signed off, the pharmacy then needed to ensure the drug arrived within the required timeframe and that the correct temperature conditions were maintained throughout shipping. When the pharmacy first decided to ship drugs, one of their most significant tasks was finding a vendor who could provide enough temperature-regulating shipping containers to mail the medications.

Finally, the drugs needed to come with the appropriate documents typically provided during in-person visits. This included things like a drug diary where patients recorded how much of a drug they took and at what time, or other instructions on how to take the drug correctly

Once the logistics were figured out and sponsors got on board, the team created workflows that allowed study teams to make formal drug shipping requests.

Over time, study teams, sponsors and patients got used to the shift, and **Kim Redic, Pharm.D.**, assistant director of the research pharmacy, says her team continues to ship more clinical trial drugs than they did pre-pandemic. She notes, however, that because of the added cost and complexity of ensuring that drugs arrive on time and in usable condition, it should happen only in specific situations in which patients are not able to receive the study medications in person.

But in those early months, when everything about the way patients accessed medicine had to be rethought, Redic says the teams understood the immense need to be flexible and to do things differently.

"We had an unquestioned lean-in," Redic says. "We knew this was what we had to do in the interest of our efforts locally for our patients but also for the greater needs of society. People didn't question or complain. They just did."

Building a Movement

Rogel investigators bring collaborative expertise to understanding statewide environmental exposures and cancer risk.

Interview by Nicole Fawcett

Celeste Leigh Pearce, Ph.D., M.P.H., wants to build more than a cohort of study participants.

She wants to create a movement. It's a movement to understand how exposures to toxic metals, industrial pollution and "forever chemicals" called PFAS are impacting the health and cancer risk of residents across Michigan.

Specifically, she wants to recruit at least 100,000 Michiganders ages 25-44 from diverse racial and ethnic backgrounds, with a focus on those who live in environmental injustice hotspots such as Metro Detroit, Flint, Grand Rapids, Kalamazoo, Lansing and Saginaw.

"As a cancer epidemiologist, the opportunity to put together a cohort that really has the potential to help us understand these important exposures is the pinnacle of what we do," says Pearce, co-principal investigator of the Michigan Cancer and Research on the Environment Study, or MI-CARES.

She is equipped with a $13 million grant from the National Cancer Institute and an expert team of collaborators from the Rogel Cancer Center and the University of Michigan School of Public Health, including co-principal investigators **Bhramar Mukherjee, Ph.D.**, and **Dana Dolinoy, Ph.D.**

Pearce, professor of epidemiology at the School of Public Health and co-lead of Rogel's cancer control and population sciences program, reflects on the project and why bringing this study to Michigan is so critical. ➔

Train bridge on the Saginaw River in Bay City during blue hour.

This is an ambitious project with a huge scope. How did it come together?

When we read the request for funding, it was really clear that Michigan was the right place to study environmental exposures and cancer risk. Michigan has had many environmental catastrophes over the decades, the most recent being PFAS and hexavalent chromium releases into the Huron River.

We also have the right people here at the Rogel Cancer Center and the School of Public Health to do this work, which made it easy to put a team together with all the relevant expertise.

In terms of size, we knew that to understand these associations, we would need a lot of people. I worked on a multi-ethnic cohort study of diet and cancer at my previous institution, which included more than 200,000 people, so I had experience and comfort with building a large cohort. We decided, go big or go home.

How do you feel about that now that you've gotten started?

It's certainly daunting! We enrolled more than 1,200 people in the first three months, which we feel good about. As we get the word out and find what recruitment strategies work best, we'll engage more communities and continue to enroll. It's about helping people understand the goals and value of the cohort but also refining our understanding of communities' needs so we can give back in a way that's meaningful to them. We want to make sure we're not just asking participants to engage but also engaging back ourselves.

How big of a problem are environmental exposures in Michigan? Why is it the place to do a study like this?

We can go all the way back to a statewide environmental exposure in the early 1970s when there was a contamination of animal feed with fire retardant. The contaminated feed was distributed all over the state and fed to animals, some of whom were slaughtered. People consumed those products and were poisoned. There are ongoing studies of the health effects of that contamination and evidence of increased risks of some cancers.

That happened almost 50 years ago, but we look back closer in time at the Flint water crisis. The health consequences there are far reaching—of course lead contamination, but we don't yet have a full understanding of all the health effects.

Then there's the Tri-Cities area of Midland, Saginaw and Bay City, as well as the River Rouge communities in Metro Detroit, which have some of the highest pollution levels in the country.

You identified six environmental injustice hotspots and plan to recruit equal numbers of Black, Hispanic, Middle Eastern and North African (MENA) and white participants. What role do racial disparities play in environmental exposures and cancer risk?

When you look broadly at exposures, communities of color are largely affected. This presents an opportunity to try to understand disparities in exposures, including across neighborhoods. In Michigan, you can see pockets of environmental injustice, which is where we are targeting our enrollment.

One important aspect of the cohort is that for the first time we'll be able to look at exposures and outcomes in the MENA community. This is often described as a hidden community because, historically, questionnaires have not asked whether people are of MENA descent. Our cohort will allow people to identify as MENA, which will give us the opportunity to understand potential health disparities in this community.

What makes this study unique?

MI-CARES is not a one-time questionnaire. Participants will give us information every year, through surveys. At the time of initial enrollment, we are also asking people to donate blood and saliva samples. It will help us understand the association between these environmental exposures and intermediate cancer markers, such as stress, inflammation and immune function. Eventually, we'll also be able to look at cancer incidence.

Our goal is to be able to look across the lifespan at critical time periods—birth, school age, puberty, young adulthood, pregnancy, menopause. To do that, you need to use a cohort, not look retrospectively, because you're capturing it in real time. This life-course approach is one of the study's key design points.

What do you hope comes from this study?

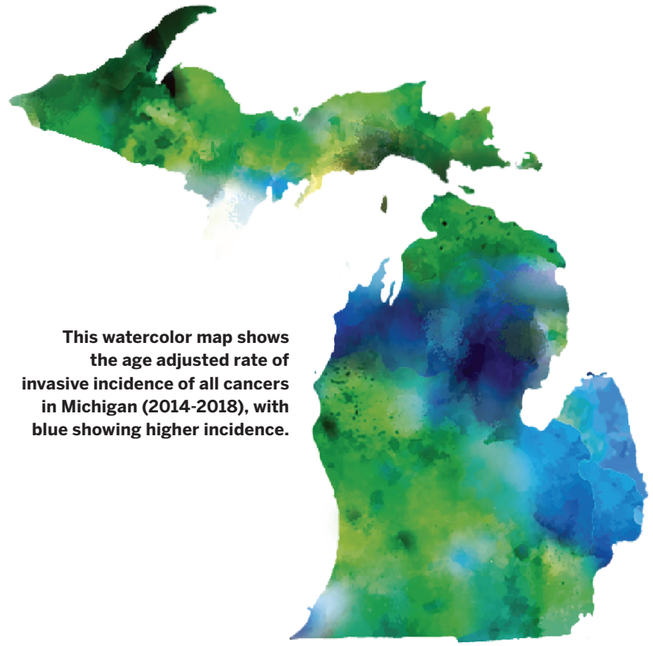
It will give us a sense of exposure distributions across communities in Michigan and help us understand differences based on racial or ethnic group and neighborhood characteristics. We also will look at the impact of environmental exposures on immune function and biologic aging. Are these exposures causing our cells to age prematurely, which could lead to cancer or other diseases?

Another opportunity is to establish smaller cohorts of cancer patients or survivors to look at environmental exposures, survival and quality of life outcomes. That's in the works for 2023.

On a broader level, I hope it's an opportunity to inform policy. The regulations around environmental pollution in Michigan and most states tend to favor businesses over individuals. Let's say there are three plants in a community all putting out pollution. If one plant asks for an override of their allowable pollution amount, the approval is based only on an evaluation of that one plant. It doesn't look at the cumulative exposure from all three plants. Right now, only New Jersey has passed legislation that looks at cumulative exposure. New York is also considering it. I would love to see legislation like this in Michigan. That's outside the scope of the cohort, but findings from the cohort can inform the policy and advocacy discussions.

At the end of the day, what I hope to show is how Michigan as a statewide community can come together and really get answers by participating in this cohort. ⊠

Learn more about MI-CARES at micares.health.



This watercolor map shows the age adjusted rate of invasive incidence of all cancers in Michigan (2014-2018), with blue showing higher incidence.

"By providing this information and these resources, we can improve their quality of life."

Lauren Ghazal, Ph.D., FNP-BC

Asking the Right Questions

Postdoctoral fellow Lauren Ghazal's training as a nurse and experiences as a cancer survivor shape her research and desire to help young adults with cancer.

By Nicole Fawcett

Lauren Ghazal, Ph.D., FNP-BC, is used to juggling multiple roles. From the time she started nursing school, she knew she wanted to be both a practicing nurse and a researcher. Then she added one more role: cancer survivor.

"It completely shifted me to studying cancer survivorship," says Ghazal of her Hodgkin lymphoma diagnosis.

"I had these views as a provider and as a researcher, and now as a young adult cancer patient. It has helped me shape research questions in a unique way because I have this embodied experience of studying what I've also lived."

Ghazal, a post-doctoral fellow in cancer care delivery research, drew from her own experience to ask questions unique to adolescent and young adult cancer survivors: Why is it so difficult to navigate the health care system? How do people manage work and careers with complications from treatment? How do they understand their health insurance and avoid medical debt?

Her research uncovered what she termed the "Survivors' Dilemma." The young adults in cancer treatment she interviewed were just beginning their careers or still completing their education. After cancer, they questioned whether they could physically or mentally do the job, whether they felt called to change career focus, and whether they could afford the cost of education or the prospect of leaving a job.

"All three of those questions completely affected one's quality of life," Ghazal says. "So, are there things we can target to mitigate financial hardship or to improve cognitive function at work?"

One avenue Ghazal would like to explore is vocational rehabilitation, where cancer survivors are connected with a counselor to help navigate questions around disclosing a diagnosis or balancing symptoms with work demands.

"These issues came up multiple times as a source of distress for cancer survivors. This is something we can help survivors with. By providing this information and these resources, we can improve their quality of life," Ghazal says. For example, an unexpected benefit of the pandemic is that remote work is more widely accepted. For a cancer survivor, calling in via Zoom could become a crucial accommodation.

The tie between financial hardship and cancer survivorship is a unique fit for Ghazal, who initially studied economics and planned to become a lawyer. A semester abroad exposed her to health care delivery systems and she came home to tell her mom, who is a nurse, that she wanted to go into nursing.

During her cancer treatment, she found herself doing late-night searches for any research on young adult cancer survivors. At that time, there was a growing body of work, some of it led by **Bradley Zebrack, Ph.D., M.S.W., M.P.H.**, professor of social work at the University of Michigan.

Today, Zebrack is one of Ghazal's mentors. She also works with the Rogel Cancer Center's recently formed Adolescent and Young Adult Oncology Team. Geared toward ages 13 to 39, the initiative includes physicians, social workers and researchers with expertise in adult, adolescent or pediatric medicine.

"I would never have gotten to this point in my research career without my cancer diagnosis and experience," Ghazal says. "Now I need to ask the right questions and make sure the work I'm doing is addressing what AYAs actually want and need. It has to have a meaningful impact."

Photo: Kathi Litwin

The Power of Why

As a child, Angel Qin's near constant refrain as she explored the world was, "Why?" Today, the medical oncologist specializing in lung cancer and researching treatment resistance still asks the question that has guided her from this early curiosity throughout her medical training.

By Staci Vernick

"It's amazing how in just a few short years, we've been able to harness the power of the immune system and use it as a tool in our armamentarium to fight cancer."

Angel Qin, M.D.

Angel Qin, M.D., is a clinical assistant professor of hematology/oncology at Rogel and a member of its Emerging Leaders Council. She leads several clinical trials that hold potential to improve the standard of care for advanced stage lung cancer as she actively engages in shaping the future of Rogel and its next generation of leaders.

Qin has always been interested in understanding the human immune system. "This phenomenal system of cells—like killer T cells and macrophages—defends us from bacteria, viruses and fungus trying to harm us on a daily basis," she says. "We have this fascinating universe inside us."

Qin was born in China and came to the U.S. when she was 8. During medical school and residency at Case Western Reserve University, Qin viewed studying clinical oncology as a privileged opportunity to connect with patients during the life-changing moment of hearing a cancer diagnosis, and to walk with them in the intimate journey that follows.

Qin says she found her true calling when she joined U-M in 2015 for a hematology/oncology fellowship. At the time, cancer immunotherapy was a nascent field, and Qin seized the opportunity to combine her interests in immunology and oncology in this exciting new direction.

"It's amazing how in just a few short years, we've been able to harness the power of the immune system and use it as a tool in our armamentarium to fight cancer," Qin says.

"We are also increasingly realizing the dream of personalized medicine in lung cancer," she says. "There are 10 approved targeted therapies and overall survival rates are improving. The problem though, is that eventually the lung cancer gets smart and overcomes whatever treatment we've offered."

This mystery of treatment resistance is the big "why" driving Qin's research today.

Co-chair of Rogel's clinical research team for lung cancer, Qin is the principal investigator on several clinical trials currently underway, including a multi-site study to determine whether adding a PARP inhibitor to standard of care combination chemotherapy and immunotherapy can improve survival in patients with metastatic non-small cell lung cancer. For her work, Qin was named a 2021 Rogel Young Clinical Investigator, an award that recognizes faculty for outstanding clinical research and a promising future in oncology.

On Rogel's Emerging Leaders Council, Qin and her colleagues work closely with cancer center leadership to advocate on behalf of early career faculty and identify high priority issues and research opportunities that will advance Rogel's mission.

"We collaborate on ways to improve the cancer center from many different perspectives—clinical operations, education, training, outreach—and put forth our vision for the institution," Qin says. To her, it is a unique opportunity to gain valuable first-hand experience in what it takes to lead one of the nation's top NCI-designated comprehensive cancer centers.

Qin also serves as the clinical lead on a large, multidisciplinary research initiative to develop more effective treatment strategies for lung cancer patients diagnosed with alterations in the ALK gene. The focus of the research, Qin says, is to understand the biological pathways that drive an individual patient's cancer—why the disease grows the way it does.

"We're trying to understand disease progression at every step from the stem cells to multi-drug resistant cells to guide personalized treatment and develop new therapies," Qin says.

Photo: Scott Soderberg, Michigan Photography

From Science to Surgery

As a trained engineer, oncologic surgeon Donnele Daley brings a technical perspective to cancer surgery.

By Eric Olsen

"It was midway through my surgical training that I started spending a lot more time taking care of cancer patients. I really enjoyed it. I feel like I develop a very meaningful relationship with cancer patients."

Donnele Daley, M.D.

As a child growing up in Jamaica and the Caribbean, **Donnele Daley, M.D.**, aspired to have a career in the applied sciences. She moved to the U.S. for college, where she studied engineering, physics and mathematics.

"My plan was to go into biomedical engineering," she says. "It wasn't until I worked with a surgeon on implant designs that I got more interested in medicine." Toward the end of her degree, she decided to go to medical school. She was particularly interested in surgery. "I was always a very technical person, and I loved the idea of being able to correct or alter anatomy for the benefit of the patient."

After earning a medical degree, during her residency in general surgery, Daley completed a postdoctoral research fellowship focusing on tumor immunology and the biology of pancreatic cancer. This sparked her interest in oncology. "I went into general surgery not really having an idea of what area I was going to specialize in. It was midway through my surgical training that I started spending a lot more time taking care of cancer patients. I really enjoyed it. I feel like I develop a very meaningful relationship with cancer patients."

Daley says the nature of cancer treatment often means she's caring for people for the rest of their lives. "It goes beyond, 'How am I going to fix this medical problem?' It's, 'How am I going to get you to your next milestone?' Like your child's graduation," she says. "It's a privilege to help patients work toward a goal. Things become valuable that perhaps weren't valuable before. And if I can somehow make those things happen for patients through my care? I find that quite rewarding."

After her surgical residency, Daley entered a fellowship in surgical oncology at Memorial Sloan-Kettering Cancer Center, where she worked closely with patients facing pancreatic and stomach cancers.

The engineer in Daley has also led her to become a proponent of machine-enhanced, or "robotic," surgery.

"We're using more advanced technology to give us the tools we need to operate more efficiently. Additionally, if patients have smaller incisions, and less pain, then they may recover more quickly," she says.

Daley says that these advances in surgical techniques represent a significant leap forward from the more invasive surgeries of the past.

"In robotic surgery, the surgeon gets many more degrees of freedom on a minimally invasive platform. You can do more complex things in small spaces that you couldn't do laparoscopically. For example, gynecological or many colorectal surgeries are performed in the pelvis, which is a very small space. And robotic surgeries can give us more technical capabilities in these small spaces. The technology is expanding the types of surgeries we can do with a bare minimum of invasiveness," she says.

"That's the real efficacy of this platform. I guess it's the engineer in me, but I think this is the direction surgery will be moving in the future."

Photo: Scott Soderberg, Michigan Photography

Improving the Future of Medicine

Nanomedicine has held promise in cancer treatment but has failed to achieve significant clinical results. Now, researchers are experimenting with new ways to design cancer treatments that rely on these tiny particles.

By Duxin Sun, Ph.D.
Charles R. Walgreen Jr. Professor of Pharmacy

Since the concept of nanotechnology was first introduced in the 1970s, it has made its mark in many everyday products, including electronics, fabrics, food, water and air treatment processes, cosmetics and drugs. Given its success across different fields, many medical researchers have been eager to use nanotechnology as a way to diagnose and treat disease. Recently, the success of some drugs using nanoparticles, such as the COVID-19 mRNA vaccines, has prompted excitement among researchers and the public about their potential use in treating various other diseases, including talks about a future cancer vaccine.

However, a vaccine for an infectious disease is not the same as a vaccine for cancer, nor as nanomedicine for cancer therapeutics. As a pharmaceutical scientist, I'm inspired by the promise of nanomedicine. My lab has worked on developing cancer treatments using nanomaterials for the past 20 years. While nanomedicine has seen many successes, some researchers like me have been disappointed by its underwhelming overall performance in cancer.

What Exactly is Nanomedicine?

We all know that nanomedicine refers to the use of materials at the nanoscale to diagnose and treat disease. The recent Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines used a nanoparticle made of lipids that help carry the mRNA where it needs to go in the body in order to trigger an immune response.

Researchers have also successfully used nanomaterials in diagnostics and medical imaging, like gold nanoparticles that form the colored band that designates a positive result in rapid COVID-19 tests and use in pregnancy tests. Magnetic resonance imaging, or MRI, also uses nanoparticles as contrast agents that help make an image more visible.

The potential of nanomedicine to improve a drug's effectiveness and reduce its toxicity is attractive for cancer researchers working with anti-cancer drugs that often have strong side effects. Several nanoparticle-based drugs have also been approved for cancer treatment. The chemotherapy drugs doxorubicin and paclitaxel use nanomaterials as a delivery mechanism to improve treatment efficacy and reduce side effects. Indeed, 65% of clinical trials using nanoparticles are focused on cancer.

This prevalence is based on the idea that nanoparticle cancer drugs could act as biological missiles that destroy tumors while minimizing damage to healthy organs. Because tumors have leaky blood vessels, researchers believe this would allow nanoparticles to accumulate in tumors. Conversely, because nanoparticles can circulate in the bloodstream longer than traditional cancer treatments, they could accumulate less in healthy organs and reduce toxicity.

Although these design strategies have been successful in mouse models, most nanoparticle cancer drugs have not been shown to be more effective than other cancer drugs. And while some nanoparticle-based drugs can reduce toxicity to certain organs, they may increase toxicity in others. For example, while nanomedicine in doxorubicin decreases damage to the heart compared to other chemotherapy options, it can increase the risk of developing hand-foot syndrome.

Improving Nanoparticle-Based Cancer Drugs

To better translate success in the lab to treatments in the clinic, my research team and I proposed a new way to design cancer drugs using nanomaterials, eventually using this strategy to develop a treatment able to achieve full remission in mice with metastatic breast cancer. We investigated ways to improve the design of nanoparticle-based cancer drugs and examined how well five approved nanoparticle-based cancer drugs accumulate in tumors and avoid healthy cells, compared to the same cancer drugs without nanoparticles. Based on our lab study's findings, we propose that designing nanoparticles to be more specific to their intended target could improve their translation from animal models to people. This includes creating nanoparticles that address the shortcomings of a particular drug, such as common side effects, and home in on the types of cells that should be targeted in each particular cancer type.

Using these criteria, we designed a nanoparticle-based immunotherapy for metastatic breast cancer. We first identified that breast cancer has a type of immune cell that suppresses immune response, helping the cancer become resistant to treatments that stimulate the immune system to attack tumors. We hypothesized that while drugs could overcome this resistance, they are unable to succeed because of insufficient accumulation in these cells. With this knowledge, we designed nanoparticles made of albumin, a common protein, that could deliver cancer drugs directly to where these immune-suppressing cells are located. The results of this study were published in *Science Translational Medicine*.

When we tested our nanoparticle-based treatment on mice genetically modified to have breast cancer, we were able to eliminate the tumor and achieve complete remission. All the mice were still alive 200 days after birth, offering hope that this treatment design could eventually translate from animal models to cancer patients to achieve long-term tumor remission.

While the field of nanomedicine has made good progress in getting drugs or diagnostics out of the lab and into the clinic, it still has a long road ahead. Learning from past successes and failures can help researchers develop breakthroughs that allow nanomedicine to live up to its promise.

A version of this article originally appeared in The Conversation.

Arul Chinnaiyan awarded prestigious Sjöberg Prize for cancer research

Arul M. Chinnaiyan, M.D., Ph.D., S.P. Hicks Professor of Pathology and Urology, was awarded the 2022 Sjöberg Prize by the Royal Swedish Academy of Sciences, which also awards Nobel Prizes.

Chinnaiyan was honored for the discovery of recurrent gene fusions in prostate cancer, a groundbreaking finding initially published in 2005 that has led to a better understanding of how prostate cancer develops and improved methods to detect the disease.

"It is a great honor to be selected for this award and to follow in the footsteps of the luminaries who have received this award in the past," says Chinnaiyan, director of the Michigan Center for Translational Pathology.

This is the sixth time the Sjöberg Prize has been awarded. It was established by businessman Bengt Sjöberg, who was diagnosed with cancer and donated two billion Swedish kronor to promote scientific research primarily focused on cancer, health and the environment. Former Sjöberg laureates include James P. Allison, Ph.D., who was awarded the Nobel Prize in Medicine in 2018.

Chinnaiyan's lab found that a prostate-specific gene called TMPRSS2 fuses with the gene ERG to drive prostate cancer development. This gene fusion, fueled by the hormone androgen, acts as an "on switch" to trigger prostate cancer. The fusion is an exquisitely specific biomarker of prostate cancer that can be detected in prostate needle biopsies and non-invasively in the urine of men with prostate cancer, which has led to improved methods for screening and diagnosing prostate cancer. It also represents a potential target for treatment, and research is ongoing to develop drugs against this genetic anomaly.

$7.6M gift launches new lung cancer research initiative

Judith L. Tam

A $7.6 million gift from Judith L. Tam and the Richard Tam Foundation has launched an accelerated research initiative at the Rogel Cancer Center to look at ALK gene mutations in lung cancer. The multidisciplinary research team seeks to understand existing treatment options and identify biological pathways that can be targeted with new approaches.

Researchers have launched a three-pronged initiative:

1. Testing patient tissue to determine how each person's cancer will respond to different therapies

2. Studying the earliest events in disease progression so that it can be detected and therapy can be adjusted accordingly

3. Developing new treatments

"We are leveraging techniques we have used to advance precision health for breast and other cancers to help patients with ALK-positive lung cancer," says lead investigator **Sofia D. Merajver, M.D., Ph.D.**, the GreaterGood Breast Cancer Research Professor at Rogel.

Rogel teams up with state's Tobacco Quitline to find new ways to help people quit menthol

A new partnership between the Rogel Cancer Center and the Michigan Tobacco Quitline will develop and test strategies to help menthol users kick the habit.

In Michigan, 40% of callers to the state's Tobacco Quitline are menthol users. Menthol cigarettes are designed to make it easier to start smoking and harder to quit. Tobacco companies have historically promoted menthol most heavily to young people, women and people who are Black.

"There is tremendous racial inequity in the use of menthol cigarettes, which has a significant impact on the health and wellness of communities across our state. Helping menthol users find the support they need to quit could save numerous lives," says **Lawrence An, M.D.**, director of Rogel's Center for Health Communications Research.

Ronald Weiser Center for Prostate Cancer established with $30M gift

Ronald Weiser

University of Michigan Regent Ron Weiser committed $30 million to Michigan Medicine to establish an innovative, patient-focused program in prostate cancer.

The Ronald Weiser Center for Prostate Cancer aims to elevate and optimize the health care experience for patients with prostate cancer and their families by investing in staff, infrastructure, technologies and education as well as research into the disease and its treatment.

"The goal is to make this center the easiest and best place to be treated for prostate cancer in the country, if not the world," says **Ganesh Palapattu, M.D.**, the George F. and Sandy G. Valassis Professor of Urology and chair of urology at Michigan Medicine.

The center will encompass state-of-the art urology, radiation oncology and radiology programs; multidisciplinary prostate cancer clinics; cutting-edge technology; highly sought-after training opportunities and a robust research program that seeks to improve the diagnosis, treatment and survivorship of prostate cancer.

U-M to lead multi-site $12M grant to study rare type of sarcoma

Scott Schuetze, M.D., Ph.D.

Laurence Baker, D.O.

An international team of researchers led by the Rogel Cancer Center received a $12.3 million collaborative Specialized Program of Research Excellence, or SPORE, grant from the National Cancer Institute to bring new insights into leiomyosarcoma.

"Rare diseases, such as leiomyosarcoma, require extraordinary collaboration to make progress. We recognized that to effectively study a rare cancer we had to assemble an outstanding international team from premier sarcoma centers," says principal investigator **Scott Schuetze, M.D., Ph.D.**, clinical professor of internal medicine.

Ten major sarcoma centers from across the world will collaborate.

"Our goal is to improve the knowledge regarding leiomyosarcoma genetics, biology and therapeutic approaches to rationally develop novel and more effective therapies. This includes combinations of different agents targeting different pathways to exploit unique vulnerabilities," says **Laurence Baker, D.O.**, professor emeritus of internal medicine and pharmacology.

Rogel appoints 4 new named professorships

The Rogel Cancer Center appointed four faculty members to named professorships:

Wicha Family Professorship in Oncology:
Joshi Alumkal, M.D.

Maisel Research Professorship in Cancer Control & Population Science:
Sarah Hawley, Ph.D., M.P.H.

Maisel Research Professorship in Oncology:
Costas Lyssiotis, Ph.D.

Maisel Research Professorship in Translational/Clinical Oncology:
Ajjai Alva, MBBS

Spotlight

Cancer Center Support Grant renewal application submitted

In May 2022, the Rogel Cancer Center submitted a grant renewal application for the National Cancer Institute's Cancer Center Support Grant, and in October, the team completed an in-person site visit with reviewers.

The grant provides significant funding to the Rogel Cancer Center and designates Rogel as a comprehensive cancer center. The proposal closely follows the strategy outlined in the Rogel Cancer Center's five-year plan around research, training and career development, community outreach and engagement, and diversity, equity, inclusion and justice.

The renewal application document contained 29 unique chapters and totaled over 2,300 pages in length. More than 60 faculty members were authors and participated in the site visit, along with dozens of staff.

The final report will be delivered in the winter with final notice of award expected in the spring.

Lok, Mukherjee elected to National Academy of Medicine

Two Rogel Cancer Center members were elected to the National Academy of Medicine, the highest honorary society in the country for researchers in the fields of health and medicine.

Anna Suk-Fong Lok, M.D., conducted the first systematic study on hepatitis B reactivation among patients receiving chemotherapy and also researches hepatitis C.

Bhramar Mukherjee, Ph.D., focuses on the development and application of statistical methods in epidemiology, environmental health, cancer research and disease risk assessment.

Anna Suk-Fong Lok, M.D.

Bhramar Mukherjee, Ph.D.

7 Rogel researchers selected as 2021 AAAS fellows

Rogel Cancer Center is home to seven members selected as 2021 fellows of the American Association for the Advancement of Science for their scientifically and socially distinguished achievements.

Veera Baladandayuthapani, Ph.D.
Mats Ljungman, Ph.D.
Sofia Merajver, M.D., Ph.D.
Melanie Ohi, Ph.D.
Patrick Schloss, Ph.D.
Katherine Spindler, Ph.D.
John Voorhees, M.D.

Rogel gift awards will support leading faculty, students

The cancer center launched a new Rogel Scholars in Cancer Health Equity program to support leading scholars in cancer health equity who are addressing cancer health equity across the basic, translational, clinical and population science research continuum. Two inaugural Rogel Scholars in Cancer Health Equity were awarded:

Katrina Ellis, Ph.D., M.P.H., M.S.W.
Elena Stoffel, M.D., M.P.H.

In addition, the following awards were funded in 2022 as part of Richard and Susan Rogel's $150 million commitment to the cancer center.

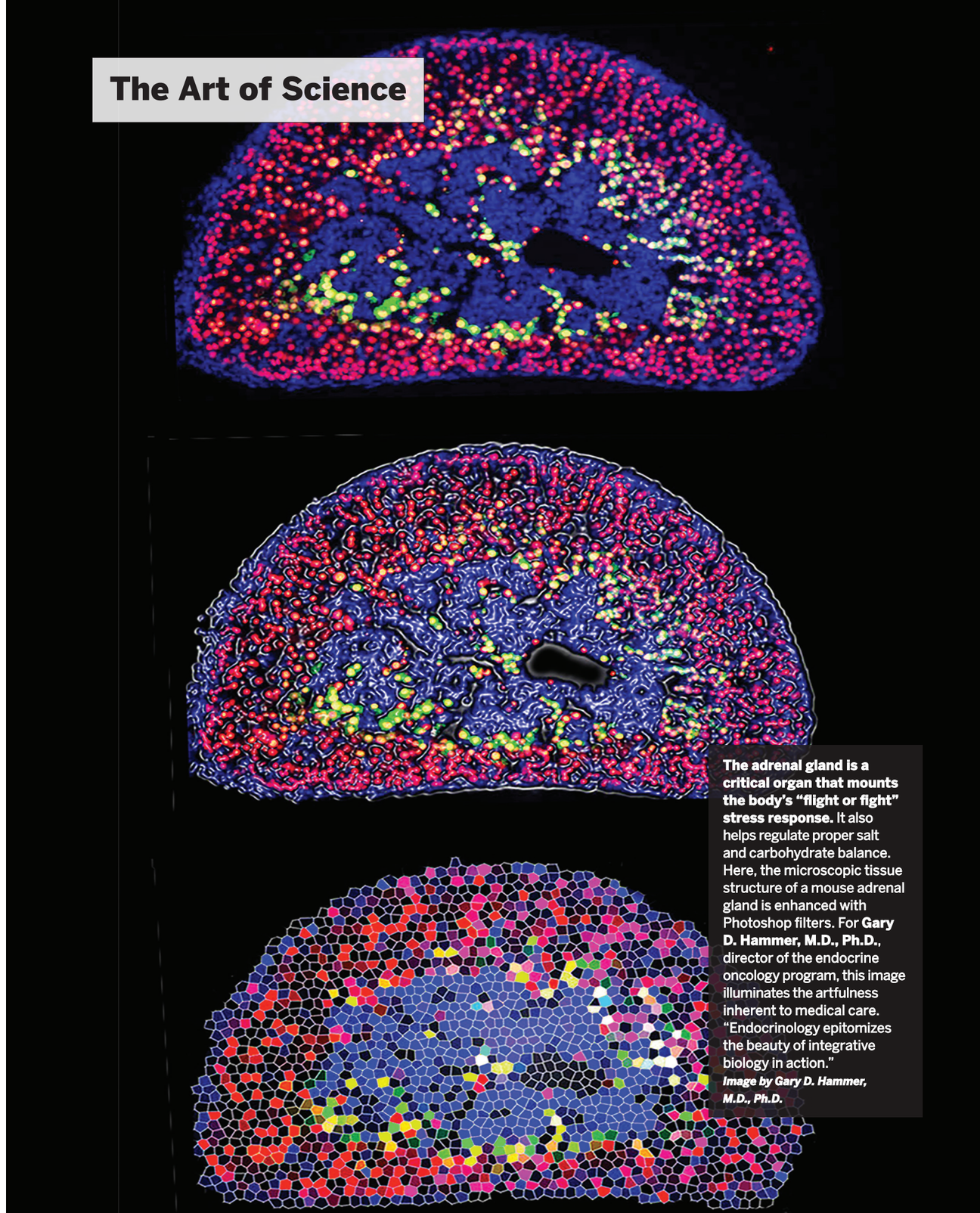
2022 Rogel Scholars:
Tomasz Cierpicki, Ph.D.
Donnele Daley, M.D.
Lesly Dossett, M.D., M.P.H.
Nisha D'Silva, B.D.S., M.S.D., Ph.D.
Amanda Garner, Ph.D.
Celina Kleer, M.D.
Goutham Narla, M.D., Ph.D.
Celeste Leigh Pearce, Ph.D., M.P.H.
Kenneth Resnicow, Ph.D.
Vaibhav Sahai, MBBS, M.S.
Simpa Salami, MBBS, M.P.H.
Ryan Wilcox, M.D., Ph.D.

2022 Clinical Research Early Investigators:
Matthew Pianko, M.D.
Andrea Franson, M.D.

2022 Medical Student Scholarships:
Holly Roberts
Cameron Harter
Abed Rahman Kawakibi

2022 Graduate Student Scholarships:
James Haggerty-Skeans
Maxwell Salvatore
Adam Olson

The Art of Science



The adrenal gland is a critical organ that mounts the body's "flight or fight" stress response. It also helps regulate proper salt and carbohydrate balance. Here, the microscopic tissue structure of a mouse adrenal gland is enhanced with Photoshop filters. For **Gary D. Hammer, M.D., Ph.D.**, director of the endocrine oncology program, this image illuminates the artfulness inherent to medical care. "Endocrinology epitomizes the beauty of integrative biology in action."
Image by Gary D. Hammer, M.D., Ph.D.

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