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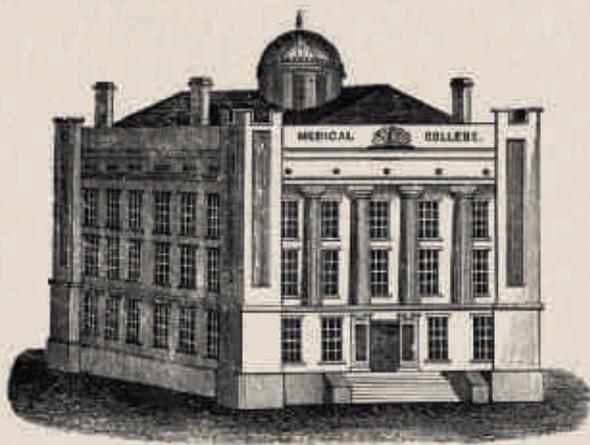


Can we
cure
cancer?



SCHOOL OF MEDICINE
CASE WESTERN RESERVE
UNIVERSITY

SUMMER | 2018



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About Medicus

Medicus is the biannual magazine of Case Western Reserve University School of Medicine. This magazine and the stories within are intended to bring to life the school's threefold mission: excellence in healthcare education, advancing discoveries from laboratories to patients, and improving the health of the community.

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Every day, Case Western Reserve University School of Medicine researchers work tirelessly to unravel the mysteries of cancer.

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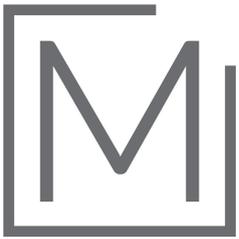


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contents



02

Dean's dialogue

Revving up Cleveland's brainpower to cure cancer



05

Searching for solutions

Developing new knowledge in biomedical research

08

From the archives

Celebrating 175 years of medical education and research

12

Solving the riddle of women's cancers

Piecing together a solution to a set of often deadly diseases



18

Stopping cancer's spread

Understanding and exploiting the mechanisms that underlie the metastatic process



24

The In-betweeners

Tailoring treatments for the unique challenges that come with adolescent and young adult cancers

30

Inside initiatives

Programs that reflect our mission



32

Education in action

Students addressing community needs

34

Honors and accolades

Recognizing our faculty

36

Left brain | Right brain

The art of science

Dean's dialogue



REVVING UP CLEVELAND'S BRAINPOWER TO BEAT CANCER

While a diagnosis can be devastating, inroads in the war against cancer are being made every day, and many of them are happening right here in Cleveland. Some of the obstacles standing in the way of a cure require figuring out how to better mobilize the human immune system to attack cancer cells. Others are based in attracting the funds necessary to bring a potential cure to fruition.

But all require the basic and clinical research environment that nurtures inquiry and collaboration.

Recently,  Pamela B. Davis, MD, PhD, dean of the School of Medicine and senior vice president for medical affairs, Case Western Reserve, sat down with  Mark Chance, PhD, professor and vice dean for research at the School of Medicine, and  Stanton Gerson, MD, professor and director of the Case Comprehensive Cancer Center, to talk about how Cleveland's collective brainpower remains poised to continue pushing the envelope in the quest to conquer cancer. The discussion was moderated by  Kay Colby, eight-time Emmy Award-winning journalist and managing producer of the Be Well Health Team at ideastream, Northeast Ohio's multiple media public service organization that includes WVIZ/PBS, 90.3 WCPN and WCLV 104.9.

Creating infrastructure... fostering innovation

Kay Colby: Dean Davis, how does the School of Medicine create an ecosystem and an environment in which to nurture basic science?

Dean Pamela B. Davis: It all starts with excellent faculty — they are our fundamental unit. And we begin by recruiting faculty who are not only highly creative, but also highly collaborative. Next, you have to provide them with the laboratory space and the necessary equipment, and you need to provide them with the opportunity to interact with other research scientists.

But it all starts and ends with the faculty member who has a drive to know something, the creativity to go after it, and the courage to pursue that problem wherever it leads. And then it's up to us to help provide the resources that allow those problems to be appropriately addressed.

This year marks the 20th anniversary that the Case Comprehensive Cancer Center received its initial designation as a comprehensive center from the National Cancer Institute. And this year also marks the year that in a review by the NCI, the Case Comprehensive Cancer Center earned an "exceptional" rating—the highest rating possible. That rating stems from the fact that the center is a consortium of three incredibly revered assets in Northeast Ohio—Cleveland Clinic, University Hospitals, and Case Western Reserve University.

KC: Dr. Gerson, how does the unique infrastructure of the cancer center help encourage cross-pollination and collaboration across disciplines?

Stanton Gerson: We bring together over 370 of our professor academic folks across the three institutions in this endeavor. It's amazing how deep the concern and interest in cancer runs in this academic community, and how many people are interested in cancer research as a topic for their academic efforts. Having the assets of the entire university, the School of Medicine, biomedical engineering, and other departments and schools within the university, as well as two major hospital systems, gives us incredible power to bring people together.

I like to use the term "transdisciplinary" research, which means, for example, having a clinician talk to a basic scientist, or having a prevention control expert talk to an imager. Our job in the cancer center is to bring these people together and ask questions in these complex manners. And we often have to do a lot of education because we speak different languages. For example, some of us might think of things in sociology terms while others think in biology terms. So sometimes we have to do "transdisciplinary" education.

The process of taking a discovery from "bench to bedside" is expensive and the federal funding environment for basic research remains unreliable. Despite the challenges, NCI reviewers gave the Case Comprehensive Cancer Center's efforts in drug discovery an exceptional rating. That high rating reflects the success of the Center's intense effort to guide promising discoveries through the so-called "valley of death"—an early stage of drug development where many potential innovations die.

KC: Dr. Chance, your role is really to help accelerate going from "bench to bedside" with a focus on getting those innovations through the "valley of death." Tell us about that.

Mark Chance: The "valley of death" didn't always exist the way it exists now. And one thing we've seen historically is that the major pharmaceutical companies — which in the past we could rely on to imagine, identify, and develop all these new therapies we want — have been withdrawing from that space. And they've been moving to the later development stages because, frankly, the early development stage is so risky.

So who's going to jump in and find these new discoveries? It's been small companies and, particularly, academic laboratories that have started getting into this space. We use our NIH funding to make early discoveries. But often that doesn't allow us to move into the next stage to design and collect rigorous preclinical data that will attract investors. We have to identify funding to do that. And the investment community has come to understand that this gap exists. And that capital has to be raised to take the most promising projects at the bench level and move them through the next stage of early stage development.

We've moved a number of drugs far enough along so what we call "professional money" now wants to take an interest. And as a result, they've moved into the commercial space. And the NCI recognized how well organized we are and the breadth and depth of our pipeline of innovation.

Home-grown discoveries... big wins

The success of the Case Comprehensive Cancer Center's focus on going from "bench to bedside" is reflected in Cleveland's contributions to innovations in cancer research and treatment as well as screening and prevention.

KC: Dr. Chance, do you have an example of an innovation you want to highlight?

MC: I have a colleague who says that every biopsy is a failed imaging opportunity. What he means is that he wants to use magnetic resonance imaging, or MRI, instead of a surgical procedure to identify how far a cancer has progressed, and use it as a basis for an appropriate treatment.

We're all familiar with magnetic resonance imaging that produces pictures of internal organs. But Mark Griswold wants to know inside the cells of those organs. So, he developed a way to take a magnetic resonance imaging scan of the chemistry inside the cells. He calls it "Magnetic Resonance Fingerprinting." It's in preliminary studies in prostate cancer. The image captures whether or not the cancer is in an aggressive form of the disease. Magnetic resonance fingerprinting has the potential to revolutionize imaging science in the treatment of cancer by indicating the level of therapy required. In some cases, it might mean watchful waiting. In others, it will indicate a more aggressive approach.

KC: Dr. Gerson, can you tell us about the work you and Dr. Sandy Markowitz are doing with Rodeo Therapeutics?

SG: You're referring to the licensing agreement with Rodeo Therapeutics. That began with Sandy Markowitz developing a concept involving a closer look at a small molecule called prostaglandin E2. Now, we knew that this hormone-like substance was important in the etiology of colon cancer and, in fact, it's now a federal recommendation to take an aspirin a day to prevent colon cancer. But it turns out, only half of us will benefit, because only half of us have the right enzyme to metabolize those prostaglandins that would be affected beneficially by aspirin.

So, he began a study to look for a molecule that would inhibit the metabolism of prostaglandin E2. After an extensive search using a technology called high-throughput screening, he came across a series of molecules that had a dramatic impact in the bowel for inflammatory bowel disease in experimental mouse model systems. He also found that these molecules had an impact on the ability of bone marrow to regenerate stem cells following ablation, encouraging bone marrow transplant recovery. This part of his work was funded by the NIH, but we needed additional funding and we received it from CWRU's Council for the Advancement of Human Health. This enabled us to develop the concept to the point where it attracted the attention of Rodeo Therapeutics, resulting in a licensing agreement. We're going into pre-clinical development now and hope to be in early phase clinical trials in 2019.

Poor outcomes... big challenges

Cleveland has some of the most glaring health disparities in the country. Many neighborhoods are plagued by high rates of poverty, obesity, and smoking — all of which are linked to poor health outcomes and reflect the social determinants of health.

KC: Dean Davis, how do you train the next generation of physicians to address the reality that, in many cases, a patient's zip code is more important than his or her genetic code?

PD: There's no question that we need to address this issue.

The very first part of the curriculum for our first-year medical students is a community block. That's the part of the curriculum where our students conduct projects in the community and learn about how environmental factors — including the stress of structural racism and poverty — interact with a person's biology to affect the health of people living in the community. And we also add in statistics and epidemiology so the students begin to think about community health quantitatively. So, we frame our entire curriculum with the concept that we all live in a community for which we all bear responsibility.

We also have in our curriculum what we call Pathways, or areas of concentration. The very first one we developed was the Urban Health Pathway. In that program, students are taught to think about how care can be delivered most effectively in the inner city, as well as how the health parameters of the inner city can be changed for the better. We encourage our students to think through these issues and how they can incorporate these concepts into their practice.

We also have developed strong graduate and Master of Public Health Programs where students are expected to look at the interaction between epidemiology and community activities. Many of our medical students do a dual degree and spend their time in those areas. And many of the projects interface with our Prevention Research Center or with our Medicaid-sponsored programs to improve health and access to care. We want to make sure that we're providing our students an experience that frames their medical education with the context of the community.

KC: How is Cleveland poised to start really moving the needle on cancer disparities as they relate to socioeconomic status, as well as different racial and ethnic groups?

SG: I have some interesting news on that. Monica Webb Hooper heads up our Office of Cancer Disparities Research. And she's completed a listening tour. It finally dawned on us maybe we didn't understand our community well enough and she went with a team of investigators and community partners from our Community Advisory Board. They went out to nine different locations. And they listened for a couple of hours to those communities and their needs. And we're taking that information and using it to help inform the next wave of research that we have. We certainly know about poverty, obesity, and tobacco as major factors and we're addressing each one of them, both in our scientific and outreach programs. **M**

Searching for solutions

BACTERIA IN THE BODY: Can the microbiome cause cancer?

Charis Eng, MD, PhD



The human body contains trillions of bacteria cells, collectively known as the microbiome. Many of these microorganisms provide benefits such as aiding digestion and lowering serum cholesterol levels. But they can cause harm as well, ranging from infections and food poisoning to respiratory illness and urinary tract infections.

Increasingly, researchers are exploring the possible role of these bacteria in the onset and progression of cancer. While tumor-causing mutations can occur randomly, evidence has been mounting that bacteria may play a role in these genetic errors. Charis Eng, MD, PhD, professor and vice chair of the Department of Genetics and Genome Sciences at Case Western Reserve University School of Medicine, professor of molecular medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, and chair of the Genomic Medicine Institute at Cleveland Clinic Lerner Research Institute, has published several recent papers exploring the possible role of bacteria as cancer-inducing agents throughout the body.

Breast cancer

Breast cancer is the second most common cancer in American women, following skin cancers. It is the second leading cause of cancer death in women; only lung cancer takes more lives each year.

While researchers have suspected a link between bacteria and breast cancer, there have been relatively few investigations. In a first-of-its-kind study, Eng, who is also a member of the Case Comprehensive Cancer Center, and colleagues found higher levels of the bacterial species *Methylobacterium* in the breast tissue of healthy women than that of women with breast cancer. Or framed alternatively, women with breast cancer have much lower levels of the bacterium than their healthy counterparts. The research team

also found that urine samples of the breast cancer patients had higher levels of gram-positive bacteria, including staphylococcus.

Head and neck cancer

Tobacco and alcohol use elevate the risk of head and neck squamous cell cancers, which see more than half a million new diagnoses every year. But with smoking and drinking rates falling and no reduction in these cancers, Eng has been scrutinizing other possible contributors.

In the largest study of the microbiome of patients with the disease to date, she and her associates compared dozens of tumors to samples of normal tissue from the same patients. They found lower levels of the bacteria genus *Actinomyces* in the tumor samples, suggesting that these bacteria may interact with genes to suppress tumor growth. This change was also more common in advanced cancers than early ones.

Tongue cancer

Squamous cell carcinoma of the tongue is an aggressive form of cancer: patients with the disease find it hard to eat, swallow food, or speak. In a pathbreaking study, Eng and colleagues, including Mahmoud A. Ghannoum, PhD, professor in the Department of Dermatology at the School of Medicine and director of medical mycology at University Hospitals Cleveland Medical Center, found that bacterial variety and richness, along with fungal richness, are significantly reduced in tumor tissue compared to matched non-tumor tissues. This raises the possibility that the bacterial profile they identified may serve as a marker for earlier diagnosis of the disease.

In all these cases, Eng notes that "additional studies are needed to confirm the findings and determine the precise nature of the relationship between bacteria and cancer. But the implications are clear: in the future, preventing and treating cancer may be aided by the targeted use of probiotics and antibiotics."



Mahmoud A. Ghannoum, PhD.

SEARCHING FOR SOLUTIONS

MOLECULAR MEDICINE: Learning the language of glioblastoma

Justin Lathia, PhD



Growing tumors are abuzz with “cellular chatter” as they release molecular signals to grow and divide. Each signal is an opportunity to intercept the signal and stop the growth of the tumor, but first, researchers must speak their language.

“We are trying to understand the language of communication that tumor cells use,” says Justin D. Lathia, PhD, assistant professor of molecular medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Case Comprehensive Cancer Center member, and associate staff at Cleveland Clinic Lerner Research Institute. In particular, Lathia’s team has been studying how glioblastoma brain tumor cells communicate.

Lathia is particularly interested in the place where adjacent tumor cells meet — called gap junctions. Gap junctions allow neighboring cells to communicate directly, akin to a handshake instead of calling across the room. “A lot of people who study cell communication think about a cell making a signaling molecule, sending it out into the environment, and having another cell pick it up. But it takes a lot of energy to do that,” he says. “Gap junctions are an energy-efficient way to allow entire tumors to be synchronous. It actually provides stability to the system.”

Lathia’s team published a series of papers showing glioblastoma cells use gap junctions to communicate across tumors. His work explained how entire tumors can quickly change characteristics, say to evade the immune system, and how specific proteins inside gap junctions help glioblastoma tumors metastasize.

Explains Lathia, “Two cells that are next to one another are physically connected by a series of channels inside gap junctions, called connexins.” There are 21 separate channel proteins (and counting) that act as glioblastoma phone lines. Lathia has outlined which connexins spread word to cancer stem cells — the stubborn cells found at the core of many tumors. Cancer stem cells are resistant to most chemotherapy, making any way to reach them appealing to drug developers.

Lathia is also studying how cancer stem cells receive growth signals. “In malignant cancers such as glioblastoma, one of the hallmarks is a large degree of cell death. This releases molecules into the environment that signal to surrounding cells that they should also die or stop dividing,” he says. “Cancer stem cells can not only persist in those environments but continue to thrive.” Lathia’s most recent work showed cancer stem cells “turn off” receptors on their surfaces to skirt such signals. Without the receptors, they can’t “hear” signals to stop dividing.

Lathia is applying lessons learned in glioblastoma to other cancers. His team recently published a *Nature Communications* paper showing breast cancer cells use connexins to assemble protein complexes required for their survival. He’s also working with Cleveland Clinic medicinal chemists to design cancer drugs that intercept signals passing through connexins — an entirely new therapeutic approach.

BIostatISTICS: Teaming up to tally brain tumors

Jill Barnholtz-Sloan, PhD



It seemed like a simple question from a mother who had just lost her son to brain cancer: “How many other children have this disease?” But the treating oncologist could not give her an answer. Neither could the American Brain Tumor Association. No one had ever totaled them up.

“Each state is mandated by law to record newly diagnosed cancer, and report it to the National Program of Cancer Registries. But ‘Brain and other Central Nervous System Tumors’ is one category. They put them all together,” says Jill Barnholtz-Sloan, PhD, Sally S. Morley Designated Professor in Brain Tumor Research, associate professor, associate director for bioinformatics at Case Comprehensive Cancer Center, and associate director for clinical informatics at the Institute for Computational Biology. “We know there are malignant and non-malignant tumors, plus dozens of subtypes in each category. This reporting is not specific enough.”

Barnholtz-Sloan has been studying — and counting — brain tumors since she was a graduate student. She is one of only a handful of brain tumor epidemiologists in the country. Six years ago, she became scientific principal investigator for the Central Brain Tumor Registry of the United States. The organization, founded 25 years ago by the grieving mother looking for answers, produces annual granular reports. One report includes, for example, 31 different brain regions where tumors occur, replete with survival rates and patient characteristics for over a hundred tumor subtypes.

The group publishes their reports in *Neuro-Oncology*, where they are consistently the most cited articles each year. Parents and doctors alike can use the free reports to answer their own questions about brain tumor incidence and prevalence. “For researchers, they provide a groundtruth that can inform scientific rationale,” says Barnholtz-Sloan.

This past fall, Barnholtz-Sloan used similar data to create some of the first assessments of global brain tumor incidence. She’s also connected brain tumor statistics to other cancers. She found 1 in 10 lung cancer patients also present with brain tumors — a number that could help foster interdisciplinary research. “I do a lot of team science. I get a lot of satisfaction out of that,” she says.

According to Barnholtz-Sloan, some of her most rewarding work sits “at the intersection of biostats and genomics.” She is currently connecting brain tumor and genomic data to develop individual clinical outcome prediction tools. “We want to know if we can identify genetic risk factors for cancers and different molecular subtypes of disease to inform treatments.”

Already her work has doubled known genetic risk factors for glioblastoma brain tumors. Barnholtz-Sloan’s studies also make it possible to predict which tumors may respond to treatment. By linking large datasets, she is not only answering questions about brain tumor incidence, but is also establishing new intersections to prevent them.

GASTROENTEROLOGY: CWRU researchers making strides against deadly GI cancers

Gastrointestinal (GI) cancer affects the digestive system and includes malignancies of the esophagus, colon, and stomach. Through the digestive process, these organs convert food to energy, supplying nutrients to sustain life. But they can also serve as the source of some of the deadliest cancers of all. Investigators at the School of Medicine are learning more about how these conditions develop — and in whom. They are also finding new ways of detecting GI cancer early, increasing the chances of prevention and successful treatment.

New tumor suppressor found

The 15-PGDH gene codes for an enzyme responsible for metabolizing prostaglandins — hormone-like substances whose functions include modulating inflammation. Sanford Markowitz, MD, PhD, the Markowitz-Ingalls Professor in Cancer Genetics and member of the Case Comprehensive Cancer Center, discovered that the 15-PGDH gene serves as a tumor suppressor in the colon and that higher expression of the gene could double as a biomarker for predicting who might benefit from taking aspirin to help prevent colon cancer.

First report of racial disparities in genetics of colon cancer

African Americans suffer and die from colorectal cancer more than any other ethnic group in the United States. Markowitz, along with his Case Comprehensive Cancer Center colleagues Kishore Guda, DVM, PhD, assistant professor, and Joseph Willis, MD, professor, found novel gene mutations associated with poorer colorectal cancer outcomes in these patients. The breakthrough could pave the way for developing biomarkers to identify those at higher risk for the disease and to tailor treatments for them, helping reduce race-based cancer disparities.

Swallowable balloon test and new biomarkers

Amitabh Chak, MD, professor, Willis, and Markowitz developed a painless five-minute outpatient test for early detection of Barrett's esophagus, a digestive disease which can be a forerunner of esophageal adenocarcinoma — a highly lethal cancer with over 80-percent mortality at five years. When diagnosed early, the cancer can be prevented, but detection requires endoscopy, an invasive, costly

test necessitating sedation, making it unsuitable for population-wide screening.

In the new test — which is much less expensive than endoscopy — patients swallow a vitamin pill-sized encapsulated balloon that swabs the esophagus. After the balloon is retrieved through the mouth, it's scrutinized for DNA abnormalities characteristic of esophageal adenocarcinoma discovered by Markowitz and Helen Moinova, PhD, instructor. This new testing approach identifies changes in the VIM and CCNA1 genes, helping support early diagnosis.

Inherited susceptibility to Barrett's esophagus and esophageal cancer

Guda, Markowitz, and Chak discovered a mutation of the VSIG10L gene associated with familial susceptibility to Barrett's esophagus and esophageal adenocarcinoma. They also found that the mutation disrupts maturation of the normal esophageal lining and uncovered additional candidate gene-alterations linked to vulnerability to these two conditions. Such findings could facilitate early prediction of risk in families, leading to prevention efforts.

First discovery of gene fusion in esophageal cancer

Genes sometimes accidentally fuse together, resulting in encoding of a single hybrid protein, instead of two separate proteins. Fusions have been found in many different solid tumors and play a major role in rapid growth of cancer cells. In the first study of its kind, Guda identified more than 20 gene fusions in esophageal adenocarcinoma tumors. In particular, fusions involving the RPS6KB1-VMP1 genes appear to alter cellular autophagy, a normal process by which old cells are replaced by new ones. Patients with this fusion did not live as long as those without it, pointing to the value of fusion markers for forecasting disease outcomes.

"Collectively, these studies have major translational and clinical significance in both creating a better understanding of how serious GI diseases develop and also supplying physicians with biomarkers to identify and closely monitor those harboring the genetic changes," says Markowitz. "Just as importantly, they open up fresh new possibilities for targeted treatments."



Left to right: Sanford Markowitz, MD, PhD, Joseph Willis, MD, Kishore Guda, DVM, PhD, Amitabh Chak, MD.

Opening of the new medical school park.

We are glad to inform you that your application for entrance to this school next fall has been accepted, on condition, of course, that your work for this year is satisfactorily completed. We shall obtain your completed record from your school office at the end of the school year.

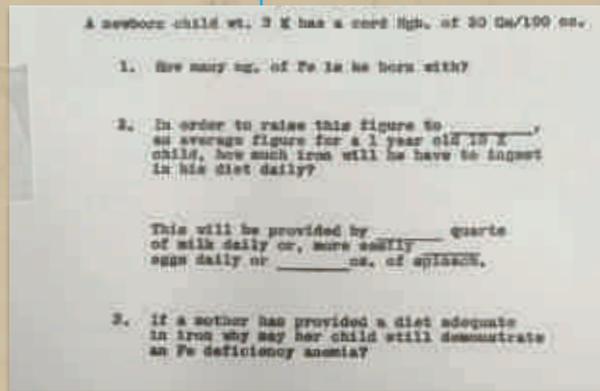


from the ARCHIVES

A question from the 1963 cardiovascular comprehensive exam. Do you know the answer?

At the School of Medicine, we have educated generations of the finest physicians and scientists who have gone on to seed the world with their own ingenuity, teaching, discoveries, and patient care.

But before they were groundbreaking scientists, trusted physicians, and beloved mentors, they were students, too, carefully navigating the same complex and rewarding journey in medicine that students undergo today. Take a look back and get a glimpse of our students' journey and the trailblazing experiences we have been offering for 175 years.



John JR Macleod, MD, 1923 Nobel Prize winner, presiding in the surgical technique laboratory in the 1920s.

* Dean Sollmann has asked me to add that in view of your recommendations and Aptitude Test ranking, he is glad to offer you an opportunity to enroll in this school. However, he advises that we should caution you that your grades in college indicate that you must apply yourself closely if you would make a success of your medical studies. He feels confident that you will do so, and that he will be fully justified in accepting you into the class.

1930s

In the first days of WRU, after students were accepted and had paid the appropriate dues and tuition, they were given "admittance cards" to the classes in which they were enrolled. This ensured the professors that students were in good standing and cleared to take the class.



A MANUAL OF EXPERIMENTAL PHYSIOLOGY

Edited By
CARL J. WIGGERS, M. D. Sc. D. F. A. C. P.
Professor of Physiology and Director of Department
School of Medicine, Western Reserve University
CLEVELAND, OHIO

1950

This lab manual was nearly 120 pages long and edited by Carl J. Wiggers, MD, who developed the Wiggers diagram that is still used to teach cardiovascular research today.

Experiment 20.
BRAIN WAVES OR ELECTROENCEPHALOGRAMS (DEMONSTRATION)

PROCEDURE. Cement electrodes on the occipital and parietal areas of the skull. Subjects should be studied while sitting or lying undisturbed in a quiet, dimly lighted room, with eyes closed. Muscles should be relaxed and the eyeballs kept still in order to avoid action potentials from eye muscles.

FROM THE ARCHIVES

Your courses will start promptly--and seriously--on Thursday, September 22nd, according to the schedule which is inclosed. You will notice that time is left for optional courses. You are free to elect these courses, unless you find it more advantageous to devote the time to your required studies or to additional library work. If you have not had Embryology in college, we strongly advise you to elect the course in Elementary Embryology offered in the first semi-semester. If you have not had Quantitative or Physical Chemistry, you will find it practically indisponable to elect the brief course which will be offered on Wednesday afternoons in the third semi-semester.

We shall be glad to welcome you here, and trust that you will find your studies interesting and enjoyable, if somewhat strenuous!



This commencement invitation marked the 50th anniversary of the medical school.



Congressman Louis A. Stokes with students discussing the significance of a 1978 Department of Health, Education and Welfare grant. The grant, which the congressman was instrumental in obtaining, was intended to identify, select, and retain minority students in the school.



48

Board of Health, Yonkers, N.Y. Entered Sept 1896 Four Year Course	1896-97	First Year Courses	Grade
		Chemistry	80
		Anatomy, Histology	75
		Physiology	60
		Histology	75
		Embryology	75
		Natural Medicine	74
		Pharmacology	
Board of Health, Yonkers, N.Y. Entered Sept 1896 Four Year Course		Chemistry	85
		Anatomy, Histology	77
		Physiology	85
		Histology	70
		Embryology	74
		Natural Medicine	80
		Pharmacology	
Board of Health, Yonkers, N.Y. Entered Sept 1896 Four Year Course		Chemistry	90
		Anatomy, Histology	80
		Physiology	70
		Histology	80
		Embryology	75
		Natural Medicine	80
		Pharmacology	
Board of Health, Yonkers, N.Y. Entered Sept 1896 Four Year Course		Chemistry	95
		Anatomy, Histology	90
		Physiology	90
		Histology	85
		Embryology	75
		Natural Medicine	75
		Pharmacology	



Solving the

RIDDLE



of Women's Cancers



Piecing together a solution to a set of often deadly diseases

by JAMIE TALAN

Each day in the research labs of Case Western Reserve University and its affiliate hospitals, hundreds of cancer scientists give their all toward finding a cure for breast and gynecological malignancies. The four researchers profiled in this article exemplify the determination, passion, and commitment of their colleagues as they tackle insidious diseases that claim the lives of approximately 70,000 women in the United States every year. The good news, however, continues to grow, offering rising hope for patients and their families.

Identifying drugs with AI

Rong Xu, PhD, lived for twenty-four years without owning a computer. But these days she doesn't go anywhere without her 13-inch laptop. This young Case Western Reserve University biomedical computer scientist is rocking the cancer world with her remarkable ability to mine mounds of data and use machine learning to redirect drugs to treat cancer.

Xu, an associate professor of biomedical informatics in the Department of Population and Quantitative Health Sciences at the School of Medicine and member of the Case Comprehensive Cancer Center, has developed software programs that rival the power of giants in the pharmaceutical industry. DrugPredict, one of her creations, has received a lot of attention from federal agencies and national cancer organizations. She's programmed it to sift through enormous data sets to look for synergy between existing medications and compounds and specific tumor types.



Rong Xu, PhD's technology could be a game-changer for cancer drug discovery.

Xu was raised in the countryside of Hunan province in China and had no electricity as a child — and of course, no computer — and yet she found herself at Peking University, its first and still only student from her village and high school. After college she came to Case Western Reserve where she pursued a degree in biology for two years. Her husband was already enrolled in a doctoral program at Stanford and she joined him in 1998. It was summer and computer science classes were open to everyone. Xu signed up and loved them. Soon she began envisioning a way to create an artificial intelligence (AI)-powered search engine that could deliver high-quality and understandable health information for patients and their caregivers.

Hoping to achieve that vision, Xu earned a master's degree in computer science and then a doctorate focusing on natural language processing, a subfield of artificial intelligence. She still

didn't own her own computer. It was at this time that she began working to develop new programs that understood free-text biomedical and clinical documents, including web pages written by people. There were many questions. For instance, could a computer learn to tell a patient everything she needs to know about her breast cancer diagnosis and recommend the drugs her doctors may want her to take?

About this time, a job offer came from Case Western Reserve — a tenure-track assistant professor position with funding to begin research in medical informatics; she snapped it up.

Soon thereafter, she developed DrugPredict. In search of effective treatments for ovarian cancer, Xu had the program scan through half a million chemicals (including thousands of federally approved drugs) and matched their characteristics with those of ovarian tumors. And it did this in a matter of minutes.

“Without these known receptors, we just don’t know what the targets are. But we will.”

The virtual hunt landed at a pain medication called indomethacin. The top 15 cancer drugs were also at the top of DrugPredict’s list on her ovarian cancer search, supporting the power of the program. Xu immediately headed down the hall to a colleague’s office with her results.

Analisa DiFeo, PhD, an ovarian cancer biologist then at Case Western Reserve and now at the University of Michigan, had written the original grant with Xu to investigate drugs for ovarian cancer. She was intrigued and tested the drug on patient-derived epithelial ovarian cancer cells and the indomethacin killed previously drug-resistant cells. DiFeo added standard chemotherapy drugs to the experimental wells filled with indomethacin and cancer cells and the cells died faster than with the pain medicine alone. It turns out that the drug works by inhibiting the Wnt signaling pathway that’s involved with the growth of tumors. The university is now talking about moving the drug into Phase I clinical trials to see if indomethacin is effective in patients.

Xu’s technology could be a game-changer for drug discovery and repurposing old drugs to treat new diseases.

“The primary advantage of drug repositioning over traditional drug development is that it starts from compounds with well-characterized pharmacology and safety profiles,” says Xu. “This significantly reduces the risk of adverse effects and attrition in clinical trials.”

She adds: “I am very driven and I don’t think about what I can’t do.” The record certainly backs her up.

Seeking insights from “Avatars”

More than thirty years ago, Ruth Keri, PhD, who was raised by her grandparents in an Appalachian community in rural Pennsylvania, accepted a job as a research assistant in Case Western Reserve’s Department of Pharmacology. John Nilson, PhD, introduced the recent Edinboro University of Pennsylvania graduate to reproductive endocrinology. Impressed by her insights and intellect, he encouraged her to apply to graduate school. She earned her PhD in pharmacology from CWRU and today is a professor at the School of Medicine and the associate director for basic research at the Case Comprehensive Cancer Center.

Keri has created several new mouse models—known as avatars in recognition of the women who donated their tumor tissues—to examine how hormones can increase breast cancer risk and to test the ability of new drugs to block the growth and spread of breast cancers.

Her background in pharmacology paid off when she began combining drugs to see whether they would work together to cause regression of tumors. She homed in on the most aggressive form of breast cancer: triple-negative malignancies that are defined by the absence of receptors that fuel most breast-cancer growth: estrogen, progesterone, and the HER-2/neu gene. Triple-negatives represent 15 to 20 percent of all breast cancers. “Without these known receptors, we just don’t know what the targets are,” explains Keri. “But we will.” In fact, she believes she has found one. Bromodomain and extraterminal domain (BET) proteins regulate gene expression and are involved in cancer pathogenesis. BET inhibitors are a new class of drugs that target BET proteins. Keri is using BET inhibitors in her mouse models and has evidence that they work to stop the growth of triple-negative breast cancer cells. She’s mapped out a novel mechanism of how the inhibitors turn off cancer genes. “If we can stop the genes from turning on, we may be able to dampen down the aggressiveness of the tumors,” she explains.

These drugs may silence the tumors, but she (and others) want them to go away completely. “Cancer is a complicated jigsaw puzzle,” says Keri. “We are trying to find similarities among different groups of tumors, and we need to figure out how to get the cells to die.” She is now working on identifying drugs that can collaborate with BET inhibitors to cause tumors to die and has a promising lead.

“I am very lucky,” she says, thinking back on her childhood, her tiny home, and Nilson’s mentorship. She now mentors others who have had challenging beginnings to become scientists who are dedicated to treating cancers. “I get to figure out what makes cancers tick and identify more powerful ways to treat these diseases.”

Ruth Keri, PhD's work targets BET proteins to turn off cancer genes.

"Cancer is a complicated jigsaw puzzle."

At the Intersection of Obesity and Cancer

Ofer Reizes, PhD, is also drawn to solving the riddle of triple-negative cancers. Reizes is an assistant professor of molecular medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, a member of the Case Comprehensive Cancer Center, and staff at Cleveland Clinic Lerner Research Institute. His journey to breast cancer researcher began with a fat mouse in a cage, which would eventually lead him to identify a so-called fat gene — leptin — as a potential target to stop triple-negative breast cancer cells in their tracks.

On his first work day at Cleveland Clinic, he noticed a sign across the street for Case Western Reserve University's Transdisciplinary Research on Energetics and Cancer program. It got him thinking. What did energetics, which is the branch of science dealing with the properties of energy and its transformations, have to do with cancer? He went to his computer and typed in "energetics and cancer," and began reading the limited but provocative literature on links between obesity and cancer. The growing prevalence of obesity in the U.S. (70 percent of adults and counting), unhealthy diets, and physical inactivity, aggregately known as "energy balance" or "energetics," is increasingly being linked with cancer incidence and mortality rates. He knew instantly that he had just stumbled onto his next research project.

Reizes was interested in the mechanisms that drive leptin's role in tumor growth. Leptin marked its entrance in the obesity research literature in 1994. Scientists have been trying to develop obesity drugs that target leptin ever since, but with limited success. Reizes decided to apply for a small pilot grant looking at the link between leptin and breast cancer.

Originally there was speculation in scientific circles that extra weight might offer some benefit to cancer patients, who often lose weight because of their disease or medications. Epidemiology research would eventually show just the opposite: obesity and cancer are linked, and Reizes wanted to figure out exactly *why* and *how*.

SOLVING THE RIDDLE OF WOMEN'S CANCERS



“We now have a potential **target** to **block** the growth of these highly aggressive tumors.”

the growth of cancer stem cells,” explains Reizes. “We now have a potential target to block the growth of these highly aggressive tumors.”

It wasn't long before Reizes found a friend and colleague in stem cell biologist Justin Lathia, PhD, an assistant professor of molecular medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, member of the Case Comprehensive Cancer Center, and associate staff at Cleveland Clinic Lerner Research Institute. In a recent paper in *Nature Communications*, the two described a survival pathway in cancer stem cells that no one had seen before. Cancer stem cells can self-replicate and spread rapidly, and this pathway could be a key in treating triple-negative breast cancer.

The researchers examined healthy breast tissue and tissue from patients with triple-negative breast cancer and found that a protein called connexin 26, which enhances cell to cell communication, has a more active presence in breast tissue from cancer patients. Could it be driving tumor progression? The protein is also more prevalent in cancer stem cells, but Reizes and Lathia found that it is inside stem cells rather than on the cell's surface, where it normally sits. They suspect that connexin's role inside the cell has a completely different function than what it does outside the cell on the plasma membrane. Studies are underway to untangle this strange new set of cellular events.

Lathia and his team also recently discovered that aggressive breast cancer cells have lost the ability to carry out direct cell-to-cell communication that is normally mediated by the connexin family of proteins.

These discoveries suggest that inhibiting Cx26 (inside the cells) and the related pathway may be a promising new strategy for stopping or preventing triple-negative breast cancer stem cells from self-renewing and spreading. They also might help identify a target for diagnostic testing that helps clinicians predict health outcomes and relapse-free survival for patients with a specific cancer type.

The two scientists also have showed that an immune regulatory protein called CD55 is abundant on the surface of endometrial ovarian cancer cells and uterine cancer cells. Work in cell culture models and animal models show that chemotherapy drugs work better when CD55 is removed from the cells. “Again, this is another potential target for developing a powerful new cancer treatment,” says Lathia. The two colleagues are now testing an investigational drug known to inhibit this CD55 signaling pathway with the cancer drug cisplatin to see if the combination treatment will be more effective at stopping the proliferation of these cancer cells.

All in all, these findings demonstrate the depth and breadth of the many efforts underway in Cleveland to bring new grounds for hope to women who suffer from cancer. [M](#)

The collaboration between Ofer Reizes, PhD, (left) and Justin Lathia, PhD, resulted in the first description of a cancer stem cell survival pathway.

He and his colleagues would soon discover that the leptin receptor (LepR) is expressed in multiple tumors. In other words, leptin is used by cancer tumors to grow and thrive. They went on to find that leptin and LepR turn on a master regulator of self-renewal in normal stem cells and in cancer stem cells. This was new and important. It was already known that leptin is expressed in the brain and in the periphery, but not in stem cells. The findings would offer the cancer world a new therapeutic target: leptin.

“No one had previously made this link between leptin and the growth of cancer stem cells,” Reizes says. “We identified a signaling pathway between the leptin receptor and the regulation of cancer stem cells, and this relationship was most robust in triple-negative cancers. We know that a high percentage of triple-negative breast cancer cells express the leptin receptor. Leptin causes



STOPPING
CANCER'S

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Susann Brady-Kalnay, PhD's work focuses on adhesion molecules to improve treatment of metastatic cancers.

in distant organs. "What we really want to do is work on invasive and metastatic tumors," she says. "Primary tumors rarely cause anyone any trouble. But once [a tumor's cells] migrate to other sites in the body, all of a sudden surgery can't effectively treat your cancer."

Brady-Kalnay is intensely focused on translating her lab's discoveries into clinical applications. But when she came to Case Western Reserve in 1995, she was strictly a basic scientist, investigating the physical connections that cells make with nearby cells. These contacts, or adhesions, are disrupted in tumors, interrupting the cell-to-cell signals that usually rein in growth and migration, making it easier for cancer cells to act independently of their neighbors.

The molecules that mediate these connections are sometimes completely lost in cancer cells. But in 2009, Brady-Kalnay discovered that in the aggressive brain cancer glioblastoma, tumor cells have a different way of untethering themselves from other cells. Searching for an adhesion molecule called protein tyrosine phosphatase mu (PTPmu) in patient samples, she discovered that tumor cells do produce the protein, but they prevent it from linking to PTPmu molecules on adjacent cells by clipping off its tip. Cells with the truncated protein can't stick to one another and are freed to move without restraint, Brady-Kalnay says.

The fragmented piece of PTPmu was remarkably specific. Brady-Kalnay's team consistently found it in tissue samples from patients with glioblastoma tumors, while it was completely absent in healthy brain tissue. Suddenly, Brady-Kalnay saw an opportunity. The fragmented protein, she thought, could act as a beacon for these highly malignant brain tumors. That would not just aid diagnosis, but it would also allow more precise surgical removal and might even be a way to deliver cancer drugs to their targets. "If you have the ability to recognize tumor cells, you can fix the problem," she says.

She and her colleagues designed a simple peptide that recognizes and binds to the telltale molecule. Alone, the peptide doesn't do much, but the team has been busily attaching it to other chemicals, from imaging agents to therapeutic nanoparticles, and demonstrating that it can guide a host of molecules to glioblastomas.

In their early experiments, the team demonstrated that in animal models, a fluorescently-tagged version of the peptide vividly lights up glioblastoma cells in the brain within minutes of injection. Following that success, Brady-Kalnay took her ideas to colleagues with expertise in clinical imaging and has worked with them to develop related versions that are visible with magnetic resonance imaging (MRI) and positron emission tomography (PET). Both reveal tumors with great sensitivity and specificity, providing clearer pictures of a metastatic tumor's spread than standard clinical imaging, which shows only anatomical abnormalities or metabolic changes within tissue. Her team's imaging tools reveal migrating tumor cells that might be missed completely using standard imaging. "We can see the cancer cells that are currently invisible with conventional imaging," she says.

read

Understanding and exploiting the mechanisms that underlie the metastatic process

by Jennifer Michalowski

Susann Brady-Kalnay, PhD, professor of molecular biology and microbiology, is frustrated by the way we diagnose and treat cancer. Detection methods are inadequate, surgery is imprecise, and treatments almost always involve distressing side effects. As she lists the many limitations of modern medicine, one can sense her impatience to deliver better options to patients.

But her frustration is counterbalanced with optimism. Taking advantage of a molecular feature of tumor cells that she discovered years ago, Brady-Kalnay has generated abundant evidence that it's possible to find cancer cells and deliver therapeutic agents with tremendous precision. Now her team is working to translate their knowledge into clinical advances that will bring real benefit to patients.

Like many cancer researchers at the School of Medicine, much of Brady-Kalnay's work is aimed at finding and treating cancer cells that have left a primary tumor and established themselves

STOPPING CANCER'S SPREAD

A high priority now is working with industry partners to move the fluorescent imaging agent, which can be used to guide surgeons in real time, into clinical trials. Brady-Kalnay and collaborators Jim Basilion, PhD, professor of biomedical engineering and radiology, and Andrew Sloan, MD, professor of neurological surgery and a neurosurgeon at University Hospitals, hope the trials will show that the enhanced imaging allows surgeons to remove more dangerous tumor cells while leaving healthy brain tissue intact.

Meanwhile, she's also working with collaborators to link her peptide to nanoparticles designed to deliver therapeutic payloads. Guided by the peptide, drug-carrying nanoparticles should migrate directly to their cancer targets inside the body. Once there, vibrations triggered by ultrasound or radiofrequency could be used to burst them open to release their contents—killing cancer cells while sparing patients the side effects of systemic chemotherapy.

Cleavage of various adhesion molecules has been observed in other cancers, so while Brady-Kalnay is still exploring the potential of her particular peptide, her approach to finding metastatic tumors may have relevance beyond glioblastoma. "My goal is to stay on this one molecule to prove what can be done with molecular recognition of cancer because it's a paradigm that can be used for all tumors," she says.

Direct delivery of drugs to their tumor targets, such as the nanoparticles Brady-Kalnay and her collaborators are working to develop, might one day reduce cancer patients' exposure to toxic chemotherapies. But for now, most people with metastatic cancer still need systemic therapies.

"If you have the ability to recognize tumor cells, you can fix the whole problem."

Once tumor cells have left a patient's primary tumor and begun to spread through the body, localized treatments like surgery and radiation become inadequate. For men with advanced prostate cancer, systemic treatment usually involves blocking or stopping the production of growth-promoting androgens. This type of hormone therapy, sometimes called medical castration, has been the standard of care for metastatic prostate cancer for more than seven decades, says physician-scientist Nima Sharifi, MD, professor of molecular medicine at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, co-leader of the Case Comprehensive Cancer Center GU Malignancies Program, and staff at Cleveland Clinic Lerner Research Institute. It usually works for a while, but prostate cancer almost always becomes resistant to this treatment.

"After tumors become resistant to castration, they used to call it androgen-independent prostate cancer," Sharifi says. "They don't use that term anymore." That's because researchers have found high levels of androgens inside such tumors. In other words, when their external androgen supply is cut off, metastatic prostate tumors start making their own.

When Sharifi's team began investigating how prostate cancer cells become so self-sufficient, their studies led them to a genetic factor that significantly impacts patients' responses to hormone therapy. In some parts of the world, the variant that they discovered—which gives prostate cancer cells a head start in overcoming standard treatments—is present in more than half of the population.

Sharifi is intent on improving treatment outcomes for patients with metastatic cancer, and he expects this genetic find to help. "One thing that I'm excited about is using this as a biomarker to identify patients who require different therapies," he says. "Right now, quite frankly, for advanced disease in prostate cancer we're not using any molecular biomarkers to drive treatment decision-making. It's just not being done."

At first, Sharifi and his team didn't know what they would find when they brought cells derived from patient tumors into the lab to test their hormone synthesis abilities. They did know that prostate cancers that progress despite hormone therapy are fueled primarily by a potent hormone called dihydrotestosterone (DHT), which, like testosterone, spurs growth via cells' androgen receptors. Their experiments showed that some prostate cancer cells were particularly well equipped to produce DHT for themselves, making it from a related hormone that remains abundant in the blood even during hormone therapy. They traced the cells' self-sufficiency to a single genetic variation.

Prostate cancer cells that efficiently manufacture their own androgens have a variation in *HSD3B1*, a gene whose enzyme product is essential for converting DHEA to DHT. All of the prostate cancer cells Sharifi's team studied produced the enzyme, but in most, it was rapidly degraded. Some cells, however, produced a much more stable version. In effect, Sharifi says, "You get much more enzyme. More enzyme means more metabolism and that means more DHT." That, in turn, allows tumor cells to thrive.

The potential impact of the variant became clear when Sharifi's team searched for it in human genome data, and found that the version of *HSD3B1* that accelerates DHT synthesis is surprisingly common. Its prevalence varies worldwide, but among Caucasians, it's carried in about half of the population.

It's now clear that variations in *HSD3B1* impact the progression of patients' disease. Sharifi's team first found a correlation between treatment outcomes and patients' *HSD3B1* genotypes using data and samples from Cleveland Clinic's prostate cancer registry. In that analysis, reported in 2016, men born with two copies of the *HSD3B1* variant experienced disease progression just two and a half years after beginning hormone therapy on average, compared to more than six and a half years of progression-free survival in men with two normal copies of the gene. Analyses of other groups of patients from Sharifi's team and others have found a similar effect. His group has also shown that among men whose prostate cancers recurred after radiation therapy to treat a primary tumor, the *HSD3B1* variant is associated with more rapid progression on hormonal therapy to metastasis. "Other groups as far away as Japan have independently validated our data, so this seems to be a biological and genetic driver of disease worldwide," he says.

The findings will be important in predicting which patients are likely to have a sustained response to hormone therapy and who might fare better with alternative treatments. Meanwhile,

Sharifi's team is already investigating ways to improve outcomes for patients with the *HSD3B1* variant. In a clinical trial currently enrolling patients at Cleveland Clinic, they are investigating how drugs that block androgen receptors impact tumors that, because of their genetic predisposition, are able to make their own androgens. "We're asking if we can reverse the bad biology associated with these genetics," Sharifi says.

For many scientists, the search for better cancer treatments starts with getting to the bottom of exactly what drives a localized tumor cell's transformation into a life-threatening metastatic one. So much has to happen for cells to establish themselves and proliferate in places they were never meant to be that there are lots of steps at which biologists and drug developers hope they might be able to intervene.

A metastasizing cell has to overcome many obstacles, says Peter Scacheri, PhD, professor of genetics and genome sciences and member of the Case Comprehensive Cancer Center. "It has to break free from the primary tumor. It has to enter the blood stream, migrate through the body, go to a distant organ, get out of the blood stream, colonize that organ, and then proliferate."

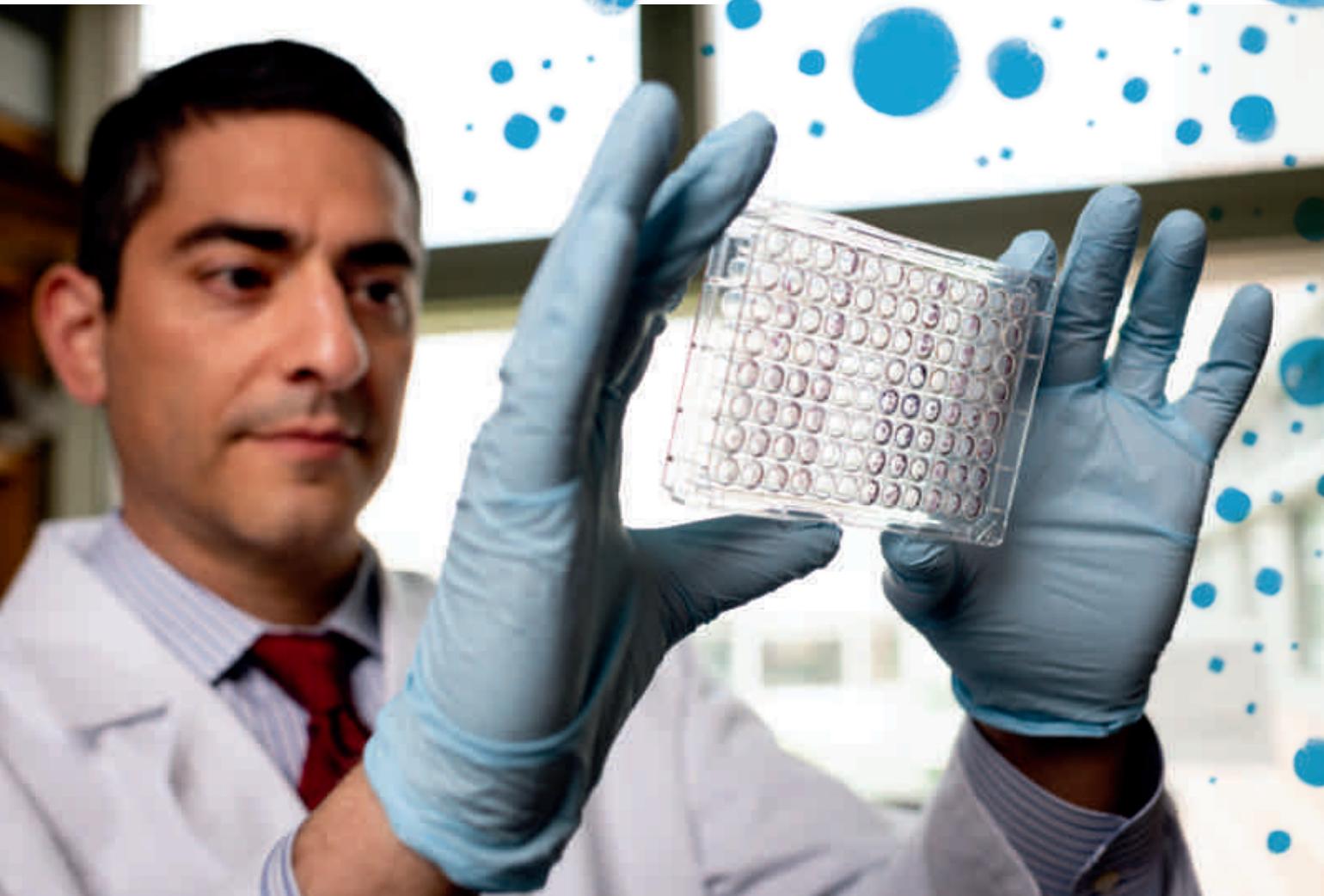
Researchers are searching for genetic changes that endow cancer cells with the capabilities to overcome these obstacles—but comparisons of metastatic tumors to the primary tumors from which they originated have turned up few recurrent mutations, Scacheri says.

That doesn't mean gene function isn't disrupted in metastatic cells, but Scacheri is convinced that their invasive nature is not entirely due to mutations in their DNA. Instead, he says, some of

the cells that primary tumors shed from their surfaces may be well suited to thrive in distant environments because of epigenetic reprogramming—that is, chemical modifications to their DNA that impact gene expression without altering the sequence of the genetic code.

Scacheri is particularly interested in enhancers, short DNA sequences that act as landing pads for activator proteins that boost gene expression when the time is right. Hundreds of thousands of these elements are scattered throughout the human genome. Scacheri likens them to dimmer switches that adjust the activity levels of the specific genes. In 2012, his team discovered that the epigenetic modifications within enhancer elements are widely disrupted in cancer cells, putting hundreds of genes under inappropriate controls. Their studies of human colorectal cancers indicated that this regulatory disarray helps drive tumor development. So, Scacheri wondered, could the same kind of changes drive metastasis?

Nima Sharifi, MD's study of an enzyme involved in hormone synthesis opens the door toward better treatment options for prostate cancer patients.



STOPPING CANCER'S SPREAD

Peter Scacheri, PhD, tracks down the role of genetic enhancers in primary and metastatic tumors.

“We think there’s **hundreds** of genes turned on by these **enhancers** in metastatic cells.”

To find out, he obtained tumor samples from patients with metastatic osteosarcoma, an aggressive bone cancer. For each patient, his team compared the enhancer landscape of a metastatic tumor that surgeons had removed from the lungs to that of the primary bone tumor.

Their studies show that hundreds of enhancers are different between primary and metastatic tumors with many of the changes falling into clusters in the genome. “Just like we saw in primary tumors, the switches are kind of all in the wrong place in metastatic tumors,” Scacheri says. “Hundreds of genes are turned on by these enhancers in metastatic cells. It’s a specific transcriptional program that gets activated and enables the cells to colonize a distant organ. You also have a whole separate program that gets silenced as well.”

Patches of the genome with particularly high concentrations of enhancer changes signaled to Scacheri and his colleagues they might be of particular importance, and they zeroed in on some of these to investigate further.

In many cases, they found that if they removed the altered enhancers, human cancer cells that were metastatic in the patient could no longer cause tumors to grow in the lungs when they were injected into mice. Preventing the enhancers from switching on their target genes had the same effect. “If you tinker with either the switches or the genes they control, you can mitigate metastasis to the lung,” Scacheri says.

Based on his team’s findings, Scacheri thinks that cells may metastasize because they are epigenetically primed to do so. “These cells are hardwired take off and thrive in a new environment,” he says.

With compelling evidence that epigenetic changes play a critical role in driving metastasis, Scacheri is hopeful that drugs that target the epigenome may be able to prevent it. His team has begun screening compounds that target epigenetic regulators, testing their ability to control the growth of metastatic cells in small samples of lung tissue. Their experiments are aimed at understanding and exploiting the mechanisms that underlie the metastatic process—with the hopes of one day passing along new knowledge that can be used to guide drug development. **M**





THE IN-BETWEENERS

Kara Lustig, 17,
was diagnosed
with cancer
two years ago.



Helping adolescents and young adults with cancer

by Scott Harris

Kara Lustig still remembers the call. Fifteen years old at the time, she was shopping with her father in their hometown of Chagrin Falls, Ohio when his phone rang. The message struck like a lightning bolt, sudden and sharp: Kara has leukemia. Get to the emergency room right away.

Just like that, what started as apparently innocuous wrist pain turned into a frightening diagnosis and more than two years of chemotherapy.

"I wondered why this was happening to me," she says. "It felt as if my life were over before it had really begun."

Flash forward to this year. In January, Kara, now 17, underwent her final treatment. She is cancer free and her prognosis is good.

"I found out I was stronger than I thought I was," she says. "And maybe I was put through this so I could change and become a better person."

Kara and many other young people are the beneficiaries of the hard work and dedication of physicians, researchers, and staff members of Case Western Reserve University School of Medicine and its clinical partners, all dedicated to addressing cancers affecting adolescents and young adults.

According to the National Cancer Institute, about 70,000 adolescent and young adult patients in the United States, defined as between the ages of 15 and 39, are diagnosed with cancer each year. This accounts for approximately five percent of all annual cancer diagnoses — about six times the number in children aged 14 and younger, although far smaller than that of older adults.

Experts say that research on these cancers has historically lagged behind that of the adult and pediatric worlds. But Case Western Reserve investigators and their clinical colleagues are changing that, earning a national reputation for addressing the imbalance.

Similarities — but also unique challenges

Research indicates that while there are often similarities, some cancers in adolescents and young adults are biologically different from versions found in other age groups. Thus research and treatment that may work for older adults has to be tailored to meet the features of a younger patient profile. Fortunately, advances in genomic medicine are enabling physicians to address this challenge. For example, genomic sequencing, which reveals the exact genetic makeup of an individual patient's cancer, is creating opportunities for patients to receive treatment based on the genetic changes found in their own individual tumors.



Another problem is that only a fraction of younger patients take part in clinical trials. In response, one of Case Western Reserve's clinical partners, University Hospitals Rainbow Babies and Children's Hospital, has become a substantial contributor to the Children's Oncology Group, the world's largest pediatric clinical trials organization, with more than 200 member-hospitals globally. "Rainbow's caregivers and physician leaders strongly encourage greater participation in clinical trials," says John Letterio, MD, professor of pediatrics at Case Western Reserve, member of the Case Comprehensive Cancer Center, and chief of the division of pediatric hematology and oncology at University Hospitals. "The research takes the form of both clinical trials and basic science investigations."

There are also differences in prevalence between adolescent and young adult cancer patients and other age groups. "Leukemia, a common childhood blood cancer, still occurs in this age group, but you see an increasing incidence of solid tumors that have limited sensitivity to chemotherapy," says Letterio. "For example, tumors known as sarcomas are among the rarest and most aggressive malignancies of bone and soft tissue. They have a high propensity for metastatic spread, creating an urgent need for more effective and alternative forms of therapy, including immunotherapy." Several Cleveland-based research teams are collaborating to uncover the unique biology of sarcomas in the 15 to 39 age cohort as well as novel therapeutic approaches to the disease.

"Another challenge is where these patients are in their lives," says Letterio. "They're not necessarily telling parents about their problems. They're studying for exams, or maybe they're parents themselves with young kids of their own and just worried about getting through the day. Maybe they'll spend six months taking an aspirin or attribute soreness to playing softball."

Cleveland's anti-cancer consortium

Case Comprehensive Cancer Center, a National Cancer Institute-designated comprehensive cancer center located at Case Western Reserve, integrates the cancer research activities of the largest biomedical research and health care institutions in Ohio — Case Western Reserve, University Hospitals, and Cleveland Clinic. Young patients diagnosed with cancer at either of these hospitals can be matched with expert adolescent and young adult clinicians and age-appropriate courses of treatment. A key vehicle is the Cleveland-based Children's Oncology Group, comprising consortium physicians who collaborate to provide diagnosis and treatment of rare cancers where a clear standard of care may be lacking. Patients are also made aware of unique clinical trials that may only be open at one of Case Western Reserve's affiliated hospitals.

"In addition to high levels of tailored care, we try to stay sensitive to the surroundings," says Letterio. "If you're in a waiting room with adults or a pediatric waiting room, the magazines are Highlights or the AARP magazine. An adolescent patient once told me that the message he got was that he didn't belong there. So our intent is to understand where patients are in their lives and create an experience that recognizes that." For example, the consortium has partnered with the Fowler family to create a specialized environment for teens and young adults with cancer: the Angie Fowler Adolescent & Young Adult Cancer Institute at University Hospitals Rainbow Babies and Children's Hospital and UH Seidman Cancer Center. Angie's Institute provides age-

appropriate inpatient and outpatient facilities and resources, such as psychosocial services, to young cancer patients. There are also opportunities to meet cancer patients in the same age group, which has become a valuable part of the healing process.

Lowering the defense shield

Alex Huang, MD, PhD, is a professor of pediatrics at the School of Medicine, director of its Pediatric Hematology-Oncology Fellowship Program, and member of the Case Comprehensive Cancer Center.

He is also a serious Star Wars fan. As he talks, Huang leavens complex scientific explanations with intergalactic metaphors. Cancer is the Evil Empire. Tumors are the Death Star. Chimeric antigen receptor T cells — specially engineered immune cells that have shown early promise in fighting cancer — are highly trained Jedi knights.

Perhaps the richest analogy is the one Huang uses to explain one of his primary avenues of research: immune checkpoints. These checkpoints, which tumor cells use to confuse the body's immune response, are akin to the defense mechanisms that protect many a Star Wars' battle station.

"It's like the shield around the Death Star," Huang explains. "Once the shield is down, one simple shot made the whole thing blow up. Healthy tumor cells, during their transformation to becoming malignant, hijack the communication signals between immune cells and the tumor cells to the point where the immune cells are fooled into thinking tumor cells are friends."

"When you put researchers in the right corridors, magic happens."

Huang is actively involved in the most intriguing avenue of research in today's cancer community: immunotherapy, or getting the body's immune system to fight cancer more effectively. The immune system distinguishes between the body's normal cells and foreign cells, allowing it to attack the latter while leaving the normal cells alone. Immune checkpoints are regulators of this immune activation. The problem is that cancer cells can manipulate checkpoints to avoid being spotted by the immune system. But drugs that target checkpoints offer hope. Huang has conducted extensive research into immune checkpoints and how to neutralize them.

"There are virtually no silos here at Case Western Reserve," Huang says. "I'm not a geneticist, but I can go down the hall and talk to someone who is. Some institutions are very top down. The difference here is that the individual investigator is the one who comes up with ideas and collaborations. I don't ever recall a time when I wanted to collaborate and someone said, 'You can't do that.' When you put researchers in the right corridors, magic happens. This is particularly important in investigating immune checkpoints, which requires many disciplines."

John Letterio, MD, and Alex Huang, MD, PhD.





What's more, there is a shared commitment to converting findings into clinical trials as quickly as possible. "We're not just studying disease," says Huang. "We're looking for a fast-track, translational angle to what we do. We're not spending 20 or 30 years in the laboratory just studying a molecule and in the end not knowing where it's going to lead us. We're constantly taking a step back and saying that in the broad scheme of things, we may not know all the details of how this works, but do we know enough to find opportunities to correct the problem through a novel treatment or re-positioning an existing one?"

Everyday cures

The word "cure" can be thorny in the cancer community.

"When I think of a cure, it's not just about the disease itself," Letterio says. "It's about the person. When I was in training 25 years ago, we used to think of patients who survived five years after treatment for cancer as cured and sent them back to their primary care doctor. But today we think much differently and stay engaged with patients' care long-term. For example, our young adult survivors of childhood cancer are participating in research that is helping us learn about possible risks for late effects of cancer therapy in children and to help patients manage these complications."

"When I think of a cure, it's not just about the disease itself, it's about the person."

Additionally, a large percentage of younger people treated for cancer don't seek follow-up care after their treatment ends. This puts them at increased risk for heart problems, infertility, and the aforementioned secondary cancers from cancer treatment. In response, the Cleveland consortium is developing specialized clinics for survivors to help mitigate this risk. "'Cure' takes on a different meaning when you attend to long-term issues such as these," says Letterio.

Kara's new life

Kara, who plans on attending Bowling Green State University this fall to become a kindergarten teacher, always loved to sing and wanted to try her hand at songwriting, too. But when she sat down to write lyrics before her illness, she never knew what to say. Now she knows. In the wake of her battle, she experienced a wave of songwriting inspiration. "I've written a lot about how to stay strong," she says. "I want to influence people positively with my songs." A recording of one of her works, *Win This Race*, is on YouTube. "I need to shine bright," she sings. "I will overcome this. I'm gonna be all right. I can't control this, but I can control my life."

In Kara's case, life imitates art. **M**

**Kara Lustig
learned to play
the ukelele while
fighting leukemia.**



Inside initiatives

At the core of drug development

Robotic arms move methodically across plastic plates covered in 384 tiny wells. They carefully drop nanoliters of drugs into each, while a nearby fluorescent microscope snaps photos. Another machine whirs in the background, rinsing and stacking plates for the next experiment.

It's all happening at the Small Molecule Drug Development Core (SMDDC) under the direction of Drew Adams, PhD, the Thomas F. Peterson, Jr., Professor in Cancer and Energy Research, assistant professor of genetics and genome sciences, and a Mt. Sinai Healthcare Foundation Scholar. The core specializes in screening libraries of drug-like molecules for new cancer therapies. Researchers commonly use the shared resource to identify molecules that could represent new medications, or new avenues for research.



Drew Adams, PhD

Says Adams, "Some people who come in want to do drug discovery. They believe they've found a new drug target, and they want to find new molecules that they can license, manufacture, and get out into the real world. That's common." Adams and his team can expose samples provided by the researchers to 50,000 different small molecules and measure interactions. They can also select other libraries to suit different purposes.

"Say you have a cancer stem cell, and you are looking for molecules that can eradicate it because the cancer stem cell is a seed that repopulates tumors after chemotherapy," offers Adams. "In addition to our library of 50,000 molecules for new drug discovery, we also have a Bioactives library. This includes molecules that are FDA-approved, or already in clinical trials, or failed clinical trials, or are coming into trials. It also includes molecules known to have a certain protein target, cellular function, or effect on a biologic pathway. You could screen all of them, and in an unbiased way, ask which of them eradicates my cancer stem cells."

The Bioactives library is often a starting point at the core, as it can open unexpected research avenues. After each screen, Adams and his team provide a list of "hits" to researchers. "You never know what you're going to find," he says. "When you get the hit list, you can go back to the library and say, okay, this molecule is an inhibitor of this particular enzyme. Nobody knew it played a role in cancer stem cell biology, but now you have a hypothesis that you can take back to your own laboratory to validate further."

The core provides free consultations to help fine tune project plans. It also offers training to research teams looking to DIY certain elements. "Different investigators have different ways they want to work with us, and we welcome that. We've had investigators want to do all the experiments themselves, and we have others who send us samples and just want the data," says Adams. "Some things people can be trained on easily; other instruments or tasks are more sensitive and we keep that within core staff."

Barely two and a half years old, the SMDDC is in high demand. New consultation requests come in weekly. The facility is open 24 hours a day, 365 days a year to users, which helps avoid bottlenecks. It's also growing—the team is currently validating an additional 50,000 small molecules that will double its screening library.

According to Adams, the SMDDC addresses a local need for high-throughput drug screening. Previously, researchers had to outsource such projects, traveling off-site for weeks at a time to perform screens or, worse, shipping precious samples across the country. The School of Medicine and Case Comprehensive Cancer Center recognized the need in 2016 and together launched the SMDDC as part of the Clinical and Translational Science Collaborative. With resources on site, Adams and his team can now walk side-by-side with researchers on the path to drug discovery. [M](#)

Partners in Brazil push research to new bounds

After a series of introductory meetings in both the U.S. and Brazil, on February 6, 2014, leadership from Case Western Reserve and Hospital Israelita Albert Einstein (HIAE) of São Paulo, Brazil, officially signed an affiliation agreement in order to build a global partnership in health education, research and innovation. Since that time there have been many conversations, visits, and two global symposiums — one in Cleveland and one in São Paulo — to share ideas and spark conversations for new international collaborations.

For Alan Levine, PhD, professor of molecular biology and microbiology at Case Western Reserve, a collaboration started one night at dinner over a Chardonnay. It was March 2017 and Case Western Reserve faculty were hosting faculty members from HIAE. Their three-day symposium in Cleveland was part of the institutions' strategic partnership in biomedical research, innovation and health education, and included faculty and researchers from the schools of medicine, nursing and engineering.

"We were chatting about science, saw the benefit of a collaboration, and immediately seized upon it," says Levine.

For years, Levine had been studying whether gut bacteria—or the microbiome—play a role in inflammatory bowel conditions. On another continent, HIAE immunologist Karina Inácio Ladislau de Carvalho, PhD, had been asking the same question. Today, both research teams are closer to finding the answer, together.

"The vast majority of research on Crohn's disease has been done in patients located in North America and Europe," says Levine. "But research emerging from Brazil offers new insights, thanks to differences in both environmental and genetic components found there."

The joint study involving the research teams of Levine and Carvalho began a few months after the Cleveland meeting. Researchers at HIAE recruited 90 Brazilian participants—30 with Crohn's taking one type of anti-inflammatory drug, 30 taking another type of anti-inflammatory, and 30 without the disease.

Since last fall, Levine's lab has been busy drawing bacterial DNA from stool collected by the HIAE lab. Levine's lab is categorizing the various populations of microorganisms in the stool and recording their diversity.

Initial data has shown clear differences in gut bacteria between all three cohorts. But that's not all.

Researchers also noticed that the microbiome was different in Crohn's patients living in Brazil and those in North America. There were some bacteria in common yet many varieties of distinct bacteria, any of which may link to the disease. "This raises new considerations," says Levine. "Maybe bacteria are less important to Crohn's than we thought. Or maybe there's a shared organism we haven't recognized yet."

The teams continue to study their collaborative findings and unravel whether differences in the microbiome are due to genetics or environment. To do that, they now are collecting bacteria samples



Gut bacteria petri dish

from healthy Brazilians living in North America to compare with bacteria from those living in Brazil.

Future scientific discoveries may lie in what's different between Americans and Brazilians. But they also may lie in what's the same.

That's what Alberto Costa, MD, PhD, professor of pediatrics and psychiatry, is counting on in his collaboration with HIAE.

Costa has been studying the use of the Alzheimer's drug memantine to improve the cognitive abilities of young people with Down syndrome. Until last November, his current study included patients mostly from Ohio. Thanks in part to the strategic partnership between Case Western Reserve and HIAE, Costa is doubling the number of participants, adding 100 more from São Paulo.

"Down syndrome affects one in 1,000 people, so that's our universe for recruitment," says Costa. "São Paulo has 10 times the population of Northeast Ohio in one-third the geographic area. They can recruit participants much more quickly and easily there."

Increased numbers mean that study results will be more robust and, therefore, more valuable for future studies.

Costa's current study is based on his earlier research at the University of Colorado, which found the memory of a small cohort of people with Down syndrome slightly improved with memantine. He expects more significant results from this larger study. If he's correct, the next and final phase of testing could be done on hundreds more participants in multiple countries.

Costa's work has attracted interest from researchers in France, England and other centers in the U.S., but collaborating with HIAE is special. Says Costa, "HIAE is a world-class medical center with premier quality-control practices. Working alongside them is a tremendous benefit."

"Our work with Einstein over the past few months is the tip of the iceberg," he says. "We anticipate many more advances in scientific research to come from our partnership." **M**

Education *in* action

Training tomorrow's cancer researchers

Student Lily Kwiatkowski spent last summer researching ovarian cancer—specifically how microRNAs interact with tumor suppressors and oncogenes. She performed DNA isolation, mice dissections and a dozen other protocols in the lab of Analisa DiFeo, PhD. She presented a poster about her project at Case Western Reserve University's Research ShowCASE in April, and soon will be a published author of a research article in medical literature.

Not bad for a junior in high school.

And she isn't the only one.

The Case Western Reserve University School of Medicine is creating opportunities for more students like Kwiatkowski, thanks to a five-year, \$2.5 million grant from the National Cancer Institute. The funds will seed a new initiative to engage underrepresented minorities from Cleveland-area schools in cancer research.

The Youth Enjoy Science (YES) program officially began this June with about 40 high school students. Some students even started early.

"There is currently a deficit in minorities engaged in scientific research," says Nathan A. Berger, MD, principal investigator of the YES program, the Hanna-Payne Professor of Experimental Medicine and director of the Center for Science, Health and Society. "To help increase workforce diversity, the YES program gives promising minority students an in-depth knowledge of biomedical lab operations and cancer research while introducing them to career possibilities. Plus, it builds their self-confidence. In two months, they go from barely whispering their names and schools in front of the group to standing up with a microphone and giving a robust scientific presentation."

As director of the Center for Science, Health and Society, Berger also has developed other youth education efforts for the School of Medicine. The Scientific Enrichment and Opportunity (SEO) program will continue alongside the YES program, while the Continuing Umbrella of Research Experience (CURE) program will be replaced by YES.

To participate in the YES program, students submit an application indicating their research interest and prospective college or university. Then they meet with faculty and guidance counselors who match them with a research laboratory in the Case Comprehensive Cancer Center.

Students work full-time in a lab during their summer break. Each student has a mentor to guide them through learning the scientific process, asking and answering important research questions, and analyzing data. When the program concludes in July, students give a poster presentation about their research.

"In my school, there is very little time for hands-on activities and labs due to our rigorous curriculum," says Kwiatkowski, who attends Cleveland School of Science and Medicine. "The program has given me a great opportunity to learn through discovery, and



Lily Kwiatkowski (right), works on an experiment with her mentor, Kelsey Polak, a graduate student in the Department of Pathology.

trial and error. After about three weeks of getting acquainted with the lab, I was performing my own experiments and contributing real data for my mentor's research."

Students aren't the only ones who benefit. Research labs garner additional productivity from their high school contributors. And graduate students get the satisfaction of mentoring younger students.

"During the poster presentations, the proudest people are the students, their families and their mentors," says Berger. "It's amazing how grad-student mentors can turn someone with very little experience into a knowledgeable future scientist."

Students are encouraged to continue working in the labs during the school year or over breaks.

"The goal is to have these students pursue biomedical research careers, so we encourage them to stick with the program for years," says Berger. "The National Institutes of Health requested that we track students for 15 years to see how our program truly affects their career paths."

Berger plans to extend the YES program beyond high school students. A middle school initiative will help educate Cleveland Metropolitan School District students on cancer prevention, risk factors and the value of cancer research. And research opportunities will be available to high school science teachers, giving them tools to engage students and raise awareness of cancer research careers.

"One of the main reasons I joined the program was to get a better idea of what I was going to pursue as a career," says Kwiatkowski. "The skills I've learned will be valuable for my future education in the sciences." **M**

First-year students serve community as patient navigators

A first-year medical student was frustrated about a miscommunication between physicians that had delayed a patient's chemotherapy. He wrote a passionate message to Heidi Gullett, MD, MPH, the Charles Kent Smith, MD and Patricia Hughes Moore, MD Professor of Education in Family Medicine, expressing his grief over the injustice and his drive to prevent future errors.

"If not now, then when? And if not me, then who?" he wrote.

That was just the response Gullett was hoping for from all students in the new Patient Navigator Program, funded by an American Medical Association ChangeMedEd grant.

Inspiring students to improve health care access and delivery is one goal of the innovative, hands-on program, an offshoot of Case Western Reserve University School of Medicine's health systems science curriculum. Mimi Singh, MD, MS, assistant dean for health systems science, leads the curriculum and co-leads the Patient Navigator Program with Gullett.

The first cohort of 35 mostly first-year students joined the program in 2017 and began putting health systems science into practice by serving as patient navigators in community health clinics.

"We hope that students understand health systems science in a deeper way because they've lived it rather than just read about it," says Gullett, who supervises the students.

From January through December, each student was paired with one patient or family at either Neighborhood Family Practice, a hub of primary care for refugees in Cuyahoga County, or the Louis Stokes Cleveland VA Center of Excellence in Primary Care Education. Students worked one-on-one with patients and families, helping them overcome barriers—language, socioeconomic, cultural and otherwise—to get the health care and other resources they need.



Patient navigator Daniel Murphy converses with patients at Neighborhood Family Practice.

In addition to spending approximately 375 hours of direct patient contact in person or by phone, each student attended monthly sessions on topics such as:

- Patient registries and how to use them to initiate population health efforts. For example, elevated leads and hepatitis B disproportionately affect the local refugee population, explains Gullett. "We have a hard time managing those folks one by one," she says. "They really need a population approach."
- Using electronic medical record systems not only as data tools, but also as communication tools. "Students learned how to work across different disciplines, such as sending the patient advocate a message, getting a behavioral health therapist involved and gathering feedback from a pharmacist," says Gullett.
- Addressing social determinants. "For example, we discussed the different elements of partnering with people living in generational poverty," says Gullett. "Language and cultural 'rules' may be different and may make navigating the world of health care difficult for some patients. We talked about how to build relationships with our patients across economic differences."

During the program, students interacted frequently with other members of their patients' care teams. They helped coordinate care and contribute insights on patients' needs.

Students practiced presenting their patients to other students in the program, exercising their oral presentation and clinical reasoning skills. At the end of the year, they used their budding communication skills to hand off their patients to a second cohort of students that began the Patient Navigator Program in January 2018. The program expanded in 2018 to include student navigators in Internal Medicine at MetroHealth.

Students apply and are selected for the program after completing Block 1 curriculum, an introduction to health systems science during their first months of medical school.

"A lot of Block 1 sensitizes our students to the profound influences of challenging social determinants, so they've been immersed in that book piece of it," says Gullett. "But when you get face-to-face with a person and hear their story, it has a very different impact."

Gullett hopes students will see the joy in building relationships with patients and the value of longevity and continuity in physician-patient relationships—a rare experience in medical education. She also hopes more students will be inspired to become change agents of health care.

"The next generation of clinicians needs to know that this is an interprofessional world of work and that we need each other," says Gullett. "Our ability to provide high-quality patient care is predicated on our ability to work together well. We need to be passionate about doing more than just plugging away and seeing a certain number of patients per day, but actually making that transformational difference." **M**

Honors and accolades

Selected items from September 2017 to April 2018

Honors

Gene Barnett, MD, professor, received the Innovation Honor for Neuronavigation Advancements from Cleveland Clinic.

S. Beth Bierer, PhD, associate professor, received the Medical Education Laureate award by the Central Group on Educational Affairs (CGEA).

Elaine Borawski, PhD, professor, was inducted into the American Academy of Health Behavior Fellows Class of 2017.

Jon Davidson, MD, FSIR, assistant professor, was inducted as a Fellow of the Society of Interventional Radiology.

Pamela B. Davis, MD, PhD, dean of the School of Medicine and senior vice president for medical affairs, Case Western Reserve University, was named a fellow of the American Association for the Advancement of Science (AAAS).

Mark Griswold, PhD, professor, was elected to the Board of Directors of the National Psoriasis Foundation.

Elaine Husni, MD, assistant professor, received the Association of Women Surgeons Kim Ephgrave Visiting Professorship at the University of Alabama.

Charles J. Malemud, PhD, professor, was named Editor-in-Chief of *Current Rheumatology Reviews*.

Richard Martin, MD, professor, was selected as the recipient of the 2018 Mary Ellen Avery Neonatal Research Award from the American Pediatric Society and the Society for Pediatric Research.

Sanford Markowitz, MD, PhD, professor, was awarded the Outstanding Investigator Award from the National Institutes of Health

Lina Mehta, MD, associate dean for admissions and associate professor, received the Exceptional Mentor Award from the American Medical Women's Association.

Suzanne Rivera, PhD, vice president for research, Case Western Reserve University, and assistant professor of bioethics, was elected to the Board of Directors of the Public Responsibility in Medicine and Research organization.

Lynn T. Singer, PhD, university deputy provost and professor, was named a fellow of the American Association for the Advancement of Science (AAAS).

Raffaella Spina, PhD, postdoctoral scholar, received the Award for Drug Discovery & Development Article of the Year from SelectScience.

Stephen Sroka, PhD, adjunct assistant professor, received the School Health Leadership Award from the American Public Health Association.

Kingman P. Strohl, MD, professor, was awarded the 2018 Excellence in Education Award for outstanding contributions in the teaching of sleep medicine from the American Academy of Sleep Medicine.

Michiko Watanabe, PhD, professor, was inducted into the American Institute for Medical and Biological Engineering College of Fellows.

Monica Webb Hooper, PhD, professor, was appointed Co-Chair of the Health Disparities Network for the Society for Research on Nicotine and Tobacco.

Grants

Kath Bogie, PhD, associate professor, received a 3 year, \$1.8 million grant from the U.S. Department of Defense.

David A. Buchner, PhD, assistant professor, received a \$400,000 grant from the National Institute of Diabetes and Digestive and Kidney Disorders.

Kevin Cooper, MD, professor, Mark Cameron, PhD, assistant professor, Nicole Ward, PhD, associate professor, Mahmoud Ghannoum, PhD, professor, Thomas McCormick, PhD, associate professor, and Rong Xu, PhD, associate professor, received a 5-year \$6.5 million grant from the National Institute of Arthritis, Musculoskeletal and Skin Diseases.

Xingjun Fan, PhD, assistant professor, received a \$2 million grant from the National Eye Institute.

Jonathan Haines, PhD, professor, and Jiri Safar, MD, associate professor, along with Thomas Wisniewski, MD, a neurologist at New York University, received \$3.95 million over five years from the National Institutes of Health, with \$2.5 million coming to Case Western Reserve University School of Medicine.

Jonathan Haines, PhD, professor, received \$7.5 million over five years from the National Institutes of Health.

Alex Huang MD, PhD, professor, and Yamilet Huerta, MD, were awarded \$186,405 in grants from the St. Baldrick's Foundation.

Alex Huang MD, PhD, professor, received a \$450,000 Basic Science grant from the Pediatric Cancer Research Foundation.

Michael W. Jenkins, PhD, assistant professor, received part of a four-year, \$9 million grant from the National Institutes of Health.

Kurt Lu, MD, assistant professor, received a \$3.9 million grant from the National Institutes of Health.

Charles J. Malemud, PhD, professor, was awarded a \$261,283 Investigator-Initiated Project Grant from Pfizer, Incorporated.

Sanjay Rajagopalan, MD, professor, received a \$2 million grant from the National Institutes of Health.

Martha Sajatovic, MD, professor, received a \$4.7 million grant from the Patient-Centered Outcomes Research Institute.

Rafick-Pierre Sekaly, PhD, professor, received an \$11 million grant from the National Institutes of Health.

John Tilton, MD, associate professor, received a 2017 Individual Biomedical Research Award from The Hartwell Foundation and will receive support for three years at \$100,000 in direct costs per year.

Anthony Wynshaw-Boris, MD, PhD, professor, received two five-year grants totaling more than \$5 million from the National Institute of Mental Health of the National Institutes of Health.

Rong Xu, PhD, associate professor, received a five-year, \$2.8 million grant from the National Institute on Aging.

Publications

Radhika Atit, PhD, associate professor, and Ahmad Khalil, PhD, assistant professor, were co-senior authors of "Wnt/ β -catenin Signaling Pathway Regulates Specific lncRNAs That Impact Dermal Fibroblasts and Skin Fibrosis," published in *Frontiers Genetics*.

Nathan A. Berger, MD, professor, was lead author of "Young Adult Cancer: Influence of the Obesity Pandemic," published in *Obesity*.

David Birnkrant, MD, professor, was lead author of "Duchenne Muscular Dystrophy Care Considerations," published in *The Lancet Neurology*.

Sudha Chakrapani, PhD, associate professor, was senior author of "Cryo-EM structure of 5-HT_{3A} receptor in its resting conformation," published in *Nature Communications*.

James Chmiel, MD, professor, Ross Myers, MD, assistant professor, and Kristie Ross, MD, associate professor, were contributors to "Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations," published in *The New England Journal of Medicine*.

Charis Eng, MD, PhD, professor, and Mahmoud A. Ghannoum, PhD, professor, were co-senior authors of "Bacteriome and Mycobiome Associations in Oral Tongue Cancer," published in *Oncotarget*.

Lilibeth Fermin, MD, clinical assistant professor, was lead author of "Pearls of Wisdom for High-Risk Laser Lead Extractions: A Focused Review," published in *Anesthesia & Analgesia*.

Darcy Freedman, PhD, MPH, associate professor, was lead author of "Systematic review of factors influencing farmers' market use overall and among low-income populations," published in *Journal of the Academy of Nutrition and Dietetics*.

Mahmoud Ghannoum, PhD, professor, was senior author of "In vitro and in vivo Evaluation of the Antifungal Activity of APX001A/APX001 Against *Candida auris*," published in *Antimicrobial Agents and Chemotherapy*.

Mark Jackson, PhD, associate professor, was senior author of "Interferon-beta represses cancer stem cell properties in triple-negative breast cancer," published in *Proceedings of the National Academy of Sciences*.

Ankur Kalra, MD, assistant professor, was lead author of "Subclinical Leaflet Thrombosis and Clinical Outcomes after TAVR: A Systematic Review and Meta-Analysis," published in *Structural Heart*.

David M. Katz, PhD, professor, was senior author of "Activation of the Medial Prefrontal Cortex Reverses Cognitive and Respiratory Symptoms in a Mouse Model of Rett Syndrome," published in *eNeuro*.

Jonathan Lass, MD, professor, was lead investigator of "Corneal endothelial cell loss 3 years after successful descemet stripping automated endothelial keratoplasty in the cornea preservation time study," published in *JAMA Ophthalmology*.

Christopher Longenecker, MD, assistant professor, was lead author of "Rheumatic Heart Disease Treatment Cascade in Uganda," published in *Circulation: Cardiovascular Quality and Outcomes*.

Robert W. Maitta, MD, PhD, assistant professor, was the author of "Clinical Principles of Transfusion Medicine."

Lin Mei, PhD, professor, was senior author of "Controlling of glutamate release by neuregulin3 via inhibiting the assembly of the SNARE complex," published in *Proceedings of the National Academy of Sciences of the United States of America*.

Helen Moinova, PhD, instructor, was lead author of "Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus," published in *Science Translational Medicine*.

Vera Moiseenkova-Bell, PhD, adjunct associate professor, was senior author of "Structural basis of TRPV5 channel inhibition by econazole revealed by cryo-EM," published in *Nature Structural and Molecular Biology*.

Nora Nock, PhD, associate professor, was lead author of "Neurobiology of substance use in adolescents and potential therapeutic effects of exercise for prevention and treatment of substance use disorders," published in *Birth Defects Research*.

Alexander Rodriguez-Palacios, DMV, PhD, assistant professor, was lead author and **Fabio Cominelli, MD, PhD, professor,** was senior author of "The Artificial Sweetener Splenda Promotes Gut Proteobacteria Dysbiosis, and Myeloperoxidase Reactivity In Crohn's Disease-Like Ileitis," published in *Inflammatory Bowel Diseases*.

Tomasz Rogula, MD, PhD, associate professor, was lead author of "Prevention and Management of Complications in Bariatric Surgery," published by Oxford University Press.

Peter Scacheri, PhD, professor, was senior author of "Positively selected enhancer elements endow osteosarcoma cells with metastatic competence," published in *Nature Medicine*.

Erika Trapl, PhD, assistant professor, was lead author of "Food melt in consumer food environments in low-income urban neighborhoods," published in *American Journal of Health Behavior*.

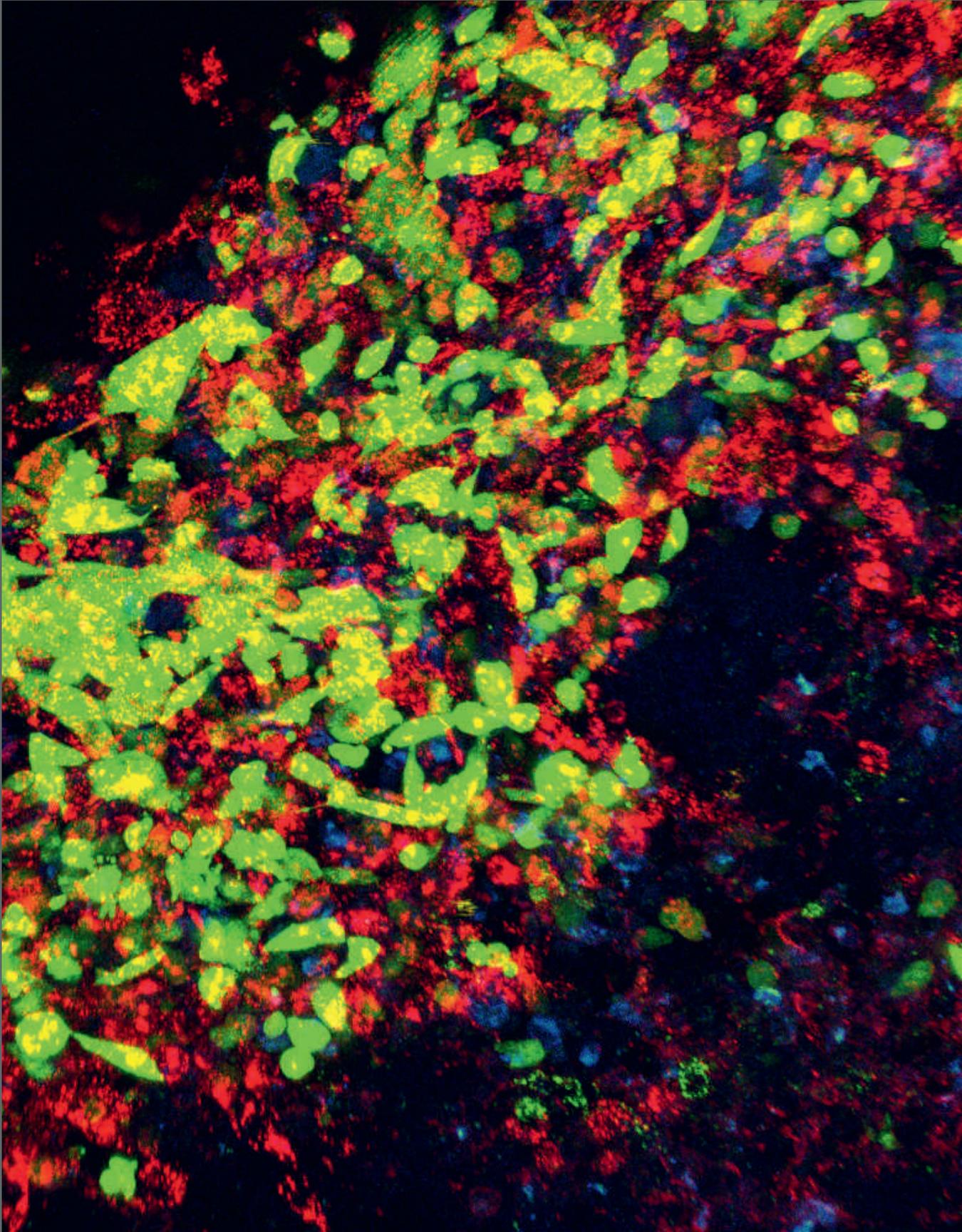
Rong Xu, PhD, associate professor, was co-senior author of "Using a novel computational drug-repositioning approach (DrugPredict) to rapidly identify potent drug candidates for cancer treatment," published in *Oncogene*.

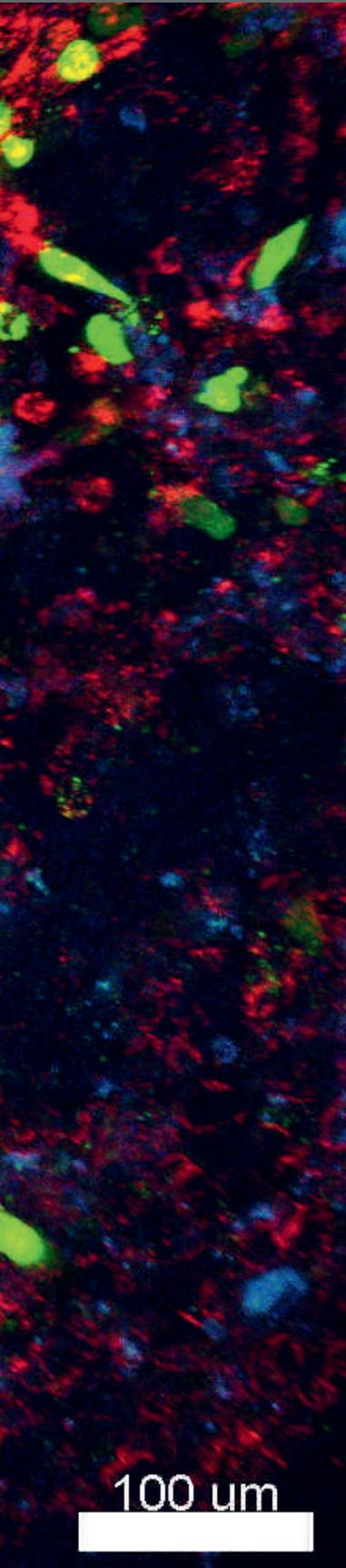
Wenquan Zou, MD, PhD, associate professor, was lead author of "Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease," published in *Science Translational Medicine*.

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Left brain | Right brain

The art of science





UNDER SIEGE

Fluorescent microscopy reveals brain tumor cells (green) under siege by immune cells (red) in a mouse model of medulloblastoma. Highly aggressive, medulloblastoma is the most common malignant brain tumor found in children.

Credit: Jay Myers, MS;
Dixon Dorand, MD, PhD;
Agne Petrosiute, MD;
Alex Huang, MD, PhD

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