In the Lab

SEQ and You Shall Find

Sequencing technology helps U-M cancer team pinpoint tumors' weaknesses


Dan Robinson

DAN ROBINSON, PH.D., IS A PORTRAITIST. But rather than rendering his subjects' appearance in ink or acrylic, the postdoctoral fellow at the Michigan Center for Translational Pathology works with the microscopic building blocks of genetic code to create detailed pictures of individual tumors.

By comparing the billions of letters in a tumor's genetic signature to DNA extracted from a patient's blood, Robinson and his colleagues can identify the tiny changes and anomalies that give rise to and fuel a patient's cancer.

"A theme that's emerging is that we have disparate cancers that share a genetic aberration that we wouldn't have known about otherwise," says Robinson. "I'm a molecular biologist, so I have a molecular portrait of a cancer — and on that level it looks like other cancers that share the same aberration."

This information can be helpful in two ways. By sequencing the tumors of patients whose cancers have failed to respond to front-line therapies, patients can sometimes be matched with existing treatments or clinical trials targeting a specific mutation. The researchers are also discovering new types of genetic irregularities, which can provide important clues for diagnosing and attacking similar cancers in the future.

As part of the center's oncology sequencing project, known as MI-ONCOSEQ — one of only a handful of similar programs across the country — researchers recently identified a gene fusion that appears to be the instigator of a rare type of cancer known as solitary fibrous tumor.

Their findings, published in *Nature Genetics*, helped to show that these tumors, which can appear in different places on the body, are being driven by the same mechanism — a fusion of the NAB2 and STAT6 genes. While, unfortunately, there were no available treatments or trials to help the 44-year-old patient in whom the fusion was first identified, when researchers examined 50 other samples from the same type of tumor, they discovered the fusion in all of them.

"Recurrence is powerful evidence that a mutation is biologically functional," Robinson says. "If they all share an anomaly, it's likely that if you can identify a therapy that's directed at it, it will have good effect across the range of these cancers."

The patient, whose samples were sequenced in 2011, was the fifth to participate in the MI-ONCOSEQ program. Today the count is well over 100.

"Genetic sequencing is extremely important with rare tumors," says oncologist Scott Schuetze, M.D., associate professor of internal medicine at the U-M and co-author of the *Nature Genetics* study. "The sequencing helps us to learn more about the disease that we can use to develop better treatments or to help diagnose the cancer in others."

Along with Robinson and Schuetze, the team included sequencing experts Yi-Mi Wu, Ph.D., and Xuhong Cao, M.S.,

DARYL MARSHKE, MICHIGAN PHOTOGRAPHY

as well as bioinformaticists Shanker Kalyana-Sundaram, Ph.D., and Robert Lonigro, M.S., plus a number of other colleagues.

Recently, the center acquired some of the latest, next-generation sequencing equipment that will cut the processing time for many clinical samples from several weeks down to about 30 hours — making the waiting time much shorter for patients who have exhausted all other options and are waiting to find out if they're a candidate for an experimental treatment.

"The technology is changing so fast," says Robinson. "Just last year I was happy with two weeks. It's amazing to think that the original reference genome, which was completed in 2003, was a 10-year project." —IAN DEMSKY

Setting a Trap for Cancer Cells

AS HUMAN BLOOD FLOWS OVER A GLASS PLATE IN A LAB AT THE U-M, individual cancer cells hitching a ride in the bloodstream stick to rough patches, just nanometers deep, that have been etched into its surface.

The new technique developed by U-M engineering and medical researchers offers a simple yet highly sensitive way to study circulating tumor cells, which are believed to contribute to cancer's ability to spread throughout the body. Unlike previous tests, the capture method doesn't require the cells to be a certain size or to express specific surface proteins.

"Our collaboration exemplifies the innovation needed for the war against cancer — team science from the lab all the way to the clinic," says Sofia Merajver (M.D. 1987, Residency 1993), Ph.D., professor of medical oncology.

When the scientists poured samples from cancer patients over the etched glass plates, the nanorough surfaces captured an average of 88 percent to 95 percent of the cancer cells — and may allow them to apprehend stealthy cancer stem cells that have evaded other techniques. One of the first uses for the technology will be to isolate live circulating tumor cells to learn more about their biological and physical properties.

Sofia Merajver

MARTIN VLOET, MICHIGAN PHOTOGRAPHY

"Understanding the physical behavior and nature of these circulating tumor cells will certainly help us better understand one of the most difficult questions in cancer biology — the metastatic cascade, that is, how the disease spreads," says Jianping Fu, Ph.D., assistant professor of mechanical engineering and of biomedical engineering, and a senior author of a paper on the technique. —ID

Research Points to New Player in Wound Healing

THE QUESTION IS NOT IF YOU prick us, will we bleed, but how will the body repair our skin? Rodent studies have shown that hair follicles are a major contributor to the generation of new skin cells. Yet, although humans are practically bald compared to most mice, our wounds still close. Similarly, glands that contribute to healing in pigs, another common laboratory stand-in, are found only in our armpits and nether regions.

A team of U-M researchers led by Laure Rittié, Ph.D., research assistant professor of dermatology in the Medical School, has discovered that the secret has been right under our noses, or rather, our skin.

"There's a good reason why these glands are under-studied — body eccrine sweat glands are absent in the laboratory animals commonly used for wound healing research," Rittié says.

Work that the team recently published in the *American Journal of Pathology* demonstrates the key role our sweat glands play in making the cells that ultimately form a new epidermis. And the matter is more than academic. Better understanding the basic mechanisms of skin repair lays the groundwork for new treatments, especially in patients with difficult wounds caused by diabetes or bed sores. —ID

In the School

Listening to our Bodies

U-M program will offer a rare opportunity for body donors to share their stories with the medical students who will dissect them

A DICHOTOMY IS EVIDENT EVEN IN the way they speak about them, the donors, the occasional slip from she to it, the acknowledgment of names bestowed upon them, even though it's against the rules. Yet it's a critical step in the education of all first-year medical students to take apart a fellow human being in pursuit of the foundational and experiential knowledge that they will rely on for their entire careers.

"It's quite a privilege to be invited by somebody and their family to dissect their body for the sake of your own education," says Michael Bohl (M.D. 2013).

At the U-M Medical School, groups of six students will each spend their entire first year with a single donor, moving together unit by unit, system by system. In a certain sense, the students will come to know him or her more intimately than anyone ever has. So, it's only natural that the experience contains an unofficial curriculum with lessons both in empathy and professional detachment.

"The very first incision is the hardest to make," says second-year student Clayton Pratt, recalling his initial introduction to the anatomy lab. "You still see the person as a person."

It was this inherent tension — the twin impulses toward connection and distance — that prompted Bohl and a fellow student to survey classmates about their feelings toward their donors, and, ultimately, to help launch a new program that will allow those who donate their bodies to the school to leave an accompanying video message.

The survey, published in *Anatomical Sciences Education* in 2011, revealed that the vast majority of students wished it had been possible for them to develop a more personal relationship with their donors — with 50 percent rating the sentiment an 8 or higher on a scale of 1-10.

Pratt and Bohl believe the video interviews could help bridge the chasm between students and donor, and allow students to understand the motivations behind a body donor's gift.

Last October, Bohl was the lead author of a second study, also published in *Anatomical Sciences Education*, which explored student and donor expectations toward a donor interview program. Nearly three-quarters of students and 81 percent of donors reported that they would participate in such a program if it existed. Notably, the paper was the first to survey and report on donor perceptions about being interviewed.

The majority of body donors who responded to the survey were warm toward the idea, with one donor even offering to help promote the program. Many reported that they would feel more at ease with the donation process knowing that their interview would accompany their gift. —IAN DEMSKY

To learn more about the Medical School's Anatomical Donation Program, visit medatmich.org/BodyDonation.

Michael Bohl and Clayton Pratt

SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

New Leader for Health Equity and Inclusion

AFTER A NATIONAL SEARCH, CARMEN R. GREEN, M.D. (RESIDENCY 1992), has been appointed as the Health System's first associate vice president and associate dean for health equity and inclusion.

Her research focuses on pain management outcomes, physician decision-making, and access to care — and has documented disparities due to age, race, gender, and other factors across the lifespan. A national leader, her work has transformed the understanding of health inequities and influenced public policy. She has worked locally and nationally to develop and enhance the health sciences pipeline for underrepresented minorities and women.

Green will lead Health System efforts to find and address inequities in care, education, and research in Michigan and beyond, and to create an equitable pathway for individuals entering health careers, especially those who are underrepresented in health care.


Carmen Green

A graduate of Michigan State University's College of Human Medicine, Green did her residency and fellowship training in anesthesiology and pain medicine at U-M, and joined the Medical School faculty as an assistant professor in the Department of Anesthesiology. Today, Green is a tenured professor of anesthesiology, with joint appointments in the Medical School's Department of Obstetrics and Gynecology and the School of Public Health's Department of Health Management and Policy. —KG

Fire Destroys Student Run Free Clinic

EARLY ON THE MORNING OF FEBRUARY 18, A FIRE RAVAGED THE STUDENT Run Free Clinic in Pinckney, Michigan. The building was declared a total loss. A story on the clinic, run entirely by U-M medical students, appeared in the fall 2012 issue.

On April 20, the clinic reopened in the Old Pinckney Community Library and plans to relocate to new permanent quarters this summer. The clinic serves uninsured Livingston County residents on Saturdays each week. To help the clinic relocate and resume its full potential, go to medatmich.org/UMclinic. —RK

New Family Medicine Chair Appointed

LONGTIME U-M PHYSICIAN Philip Zazove, M.D., has been named chair of the Medical School's Department of Family Medicine.


Philip Zazove

A faculty member in the department for more than 20 years, Zazove began his new position as the George A. Dean, M.D., Chair of Family Medicine in December 2012.

"Dr. Zazove has an exceptional record of accomplishment throughout his academic career at the U-M," says James O. Woolliscroft, M.D., dean of the Medical School.

"His expertise and experience are invaluable assets that will contribute to the department's distinguished history of serving as a model for primary care education and research and improving the health of our patients, their families, and our communities," he adds.

Zazove is also well-known for his remarkable personal story that led to becoming just the third deaf doctor in the country. At age four, in 1955, he was diagnosed as profoundly deaf — but his parents made a radical decision to keep him in mainstream education and encourage him to pursue his dream to be a doctor. —BM

LEFT: MARTIN VLOET, MICHIGAN PHOTOGRAPHY
RIGHT: SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

In the Clinic

Seizing the Seizures

Advanced technique to pinpoint seizure source helps musician get his groove back


Simon Glynn

MUSICIAN PAUL SKRIPNIK DIDN'T like to walk on the sidewalk. He mainly stuck to the grass for fear he would crash to the ground if a seizure unexpectedly struck. Living with epilepsy prevented the 29-year-old composer from attending music school and even from driving.

Yet following successful treatment at the U-M, Skripnik kicked off 2013 by playing a concert of newly composed music in Grand Rapids as he marked nearly a year and a half seizure-free. Skripnik was not only celebrating newfound freedom, but also raising money for future epilepsy research.

After years spent trying unsuccessfully to control his condition with medications, Skripnik came to the U-M to find out whether he might be a candidate for surgical intervention. A big part of the answer lay in figuring out what part of his brain was spawning the convulsions.

The source of every patient's seizures is different, and the U-M epilepsy team uses a number of tools to find a patient's seizure "focus," explains Simon Glynn, M.D., assistant professor of neurology in the U-M Medical School. Doctors homed in on Skripnik's seizures with a battery of tests, including monitoring the electrical activity of his brain with sensors placed around his head, and taking images with MRI and PET scanners.

The tests, however, only provided a general map of the seizures' location. To pinpoint the exact source, doctors had to open Skripnik's cranium and place an array of electrodes known as a grid over two candidate areas — an advanced procedure available at only a small number of medical centers. Skripnik learned that the part of his brain that was generating his seizures was extremely close to areas that controlled his ability to play piano and percussion, not to mention other tasks requiring manual dexterity and higher brain function.

"With Paul, we were able to develop a hypothesis of where to place the grids for intracranial monitoring, and using them we were able to define a safe area to resect," says Glynn. "If we had not had such precise information, all of his composing and performing ability, even his language ability, would have been at risk from the resection of the seizure focus."

In choosing the U-M, Skripnik joined the roughly 3,000 epilepsy patients who turn to the U-M for care each year, and the 100 who undergo surgery. The U-M team has earned the highest level of distinction from the National Association of Epilepsy Centers.

For a week, the grids in Skripnik's head collected data about electrical activity in the two regions. This allowed Oren Sagher, M.D., a professor of neurological surgery at the U-M, who led the surgical team that performed both operations, to zero in on a spot in the musician's left parietal lobe and remove the smallest possible amount of brain tissue.

Today Skripnik is not just back to writing and playing music — being seizure-free has changed his life.

"Living without seizures is a dream for all who experience epilepsy," he says. "My thinking skills, memory, and faculty for music have improved steadily since the operation. I am overjoyed to be rid of that part of my brain."

—KARA GAVIN

SCOTT SODERBERG, MICHIGAN PHOTOGRAPHY

Lowering Maternal Mortality

WOMEN IN AFRICA ARE 250 TIMES more likely to die from pregnancy complications than women in North America. And a leading cause of death in areas without access to advanced care is postpartum hemorrhage.

Although uterine compression to stanch bleeding is commonly taught, a recent U-M study conducted in Ghana found that a two-person team approach is likely far superior to the standard, single-provider technique.

Timothy R.B. Johnson, M.D. (Residency 1979), the Bates Professor of the Diseases of Women and Children and chair of the Department of Obstetrics and Gynecology, and Pamela Andreatta, Ph.D., an associate professor of medical education and ob/gyn, found that individuals working alone were unable to fully compress the uterus of a specialized simulator and became tired after about two minutes. Meanwhile, pairs — one applying external pressure and one internal — were able to light and maintain all six of the pressure-sensitive simulators' lights for the full five-minute test.

"Our findings suggest that it may be time to reconsider how the technique is taught — from rural, low-income settings up to advanced tertiary care centers," says Andreatta. She added that further studies are needed to determine how well the teams can sustain pressure not only for the recommended five to 30 minutes, but also for the 30 to 90 minutes that may be required to transport a patient to the hospital from a remote area.—ID

Deadly Transplant Side Effect Cut in Half

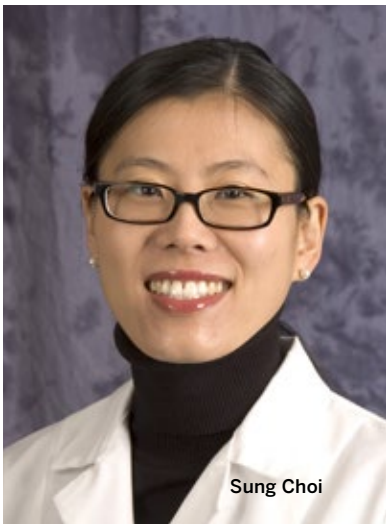
A FREQUENTLY DEADLY SIDE EFFECT OF BONE MARROW TRANSPLANTS known as graft-versus-host disease (GVHD) might be significantly reduced using a new drug, researchers at the U-M Comprehensive Cancer Center have found. The findings are the culmination of more than eight years of laboratory and clinical research.

In the first study in patients, when the drug vorinostat was given along with standard treatments after a bone marrow transplant, only 21 percent of patients developed GVHD. Typically, more than 40 percent of patients acquire the condition.

Vorinostat is already approved to treat certain types of cancer, but senior study author Pavan Reddy, M.D., associate professor of internal medicine in the U-M Medical School, found in the lab that the drug had anti-inflammatory effects and reduced GVHD in experimental models. Researchers hypothesized that it might be useful in preventing GVHD, a condition caused when donor T cells attack host tissues, including the skin, liver and gastrointestinal tract.

"Graft-versus-host disease is the most serious complication from transplant that limits our ability to offer it more broadly. Current prevention strategies have remained mostly unchanged over the past 20 years," says the study's lead author Sung Choi, M.D. (Fellowship 2005), assistant professor of pediatrics at the U-M. "This study has us cautiously excited that there may be a potential new way to prevent this condition."—NF

Pavan Reddy



Sung Choi

LEFT: ERIC BRONSON, MICHIGAN PHOTOGRAPHY
RIGHT: FILE PHOTO

In the Clinic

Renoir, a Model for Contemporary Arthritis Patients

FRENCH PAINTER PIERRE-AUGUSTE RENOIR IS celebrated as one of the greatest artists of the modern era, but looking at his impressionistic tableaus and charming portraits, one would never guess that during the last 20 years of his productive career, he was plagued by rheumatoid arthritis. Ultimately the condition left him unable to pick up a brush without help, but he didn't let that stop him from working.

In a recent issue of the journal *Hand*, research associate Evan Kowalski and Kevin Chung, M.D. (Residency 1994, M.P.H. 1997), the Charles B. de Nancrede Professor of Surgery, argue that Renoir's physical and emotional coping strategies can serve as models for today's arthritis patients. "The mindset of the patient is a huge determinant for the way this condition affects their life," says Chung. "It is clear that Renoir's strategies helped him to stay positive and productive throughout his long struggle with arthritis."

After he became wheelchair-bound, Renoir continued to work on large canvasses using a system with a pulley to bring each section to his level. Renoir also embodied some of the same emotional advice offered to patients today: accepting his increasing limitations, reclaiming control where he could, and reframing the situation to find fulfillment.

"Renoir did everything in his power to prevent his impairment from turning into a disability," says Kowalski. —ID

The Brain's Role in Fibromyalgia

THE DISCOMFORT ASSOCIATED WITH FIBROMYALGIA MAY BE CAUSED BY A problem with the way the brain processes pain stimuli, U-M researchers are learning. A recent study led by Richard E. Harris, Ph.D., assistant professor of anesthesiology and research assistant professor in rheumatology, found that some people with fibromyalgia have a decrease in their brain's opioid receptor binding and this was associated with an exaggerated brain response to pain. One consequence may be that these patients are harder to treat with opioid painkillers — moreover, they may even be made worse by taking them. "Although we have known for some time that the brain is a key player in fibromyalgia, we are just now starting to learn about the role that this disruption of pain regulation may play," says Harris. —ID

Health Briefs

A muscle regulating protein called troponin appears to be a powerful predictor of heart attack and death following non-cardiac surgery. Calling it a "golden opportunity" to reduce risk, U-M's Vineet Chopra, M.D. (M.S. 2011), assistant professor of internal medicine, and Kim Eagle, M.D., director of the Cardiovascular Center, outline a strategy in the *Journal of Hospital Medicine* for using the marker to improve outcomes.
medatmich.org/troponin

Friends and relatives of those with bipolar disorder often say they can hear changes in their loved one's voice that indicate an incipient mood shift. Now researchers at the U-M, armed with smartphones and voice analysis software, hope to quantify and map the patterns of speech that may precede changes detectable by the unaided ear. If successful, the approach could have significant implications for prediction and detection of the mania and depression that are the hallmarks of bipolar disorder. The project is a collaboration between Melvin McInnis, M.D., and Masoud Kamali, M.D., from the U-M Depression Center, and Zahi Karam, Ph.D., and Emily Mowers Provost, Ph.D., from the College of Engineering.
medatmich.org/BPvoice

PIERRE-AUGUSTE RENOIR, SELF-PORTRAIT (1910)