S T A N F O R D

M E D I C I N E

Issue 1 / 2020

special report

CRACKING CANCER'S CODE

New reasons for hope

Light amid the darkness
Cancer is no longer always a death sentence

Navigating survival
Teens and young adults are especially at risk

In a fog
Chemo brain is real

Connections
Realizing the power of empathy

Digging deep
Uncovering genetic solutions

Lucy Kalanithi
Five years later, love lives on

plus

The perfect surgery
Motion tracking to define success

Discovering Precision Health
An excerpt from the new book by Dean Lloyd Minor, MD

STANFORD MEDICINE

Issue 1 / 2020

TWINS UNLEASHED

FORMERLY CONJOINED, THE GIRLS ARE FLOURISHING

Formerly conjoined twins Erika and Eva Sandoval are lively 5-year-olds with a lot to say. I experienced this firsthand when I spoke recently with them and their mom, Aida Sandoval. She put me on speaker phone, and I asked the girls what they like about kindergarten, which they attend near their family's home in Redding, California.

"I like going on the slide!" Eva shouted.

"I like choice time!" Erika responded, matching Eva's zeal.

"I like choice time, too!" Eva yelled.

The twins' enthusiasm for exploring the joys of kindergarten is just one indicator of how far the girls have come since they were born at Lucile Packard Children's Hospital Stanford in 2014 and their anatomy resembled two people above the rib cage, merging almost to one below the bellybutton.

The twins were separated in a 17-hour, 50-person procedure performed at the hospital in December 2016 that required months of planning. There was no guarantee that both girls would survive surgery and recovery. If they did, each twin would have one functional leg and would lack many abdominal muscles; at first, their surgeon wasn't sure they'd be able to sit without support. Everything from how much blood the twins might lose to how they'd handle the emotional impact of being separated had to be figured out one step at a time.

Three years after a 17-hour, 50-person surgery separated conjoined twins Eva, left, and Erika Sandoval, the 5-year-olds are energetic, curious kindergartners with distinct personalities.

KEVIN FISCUS

Sandoval and her husband, Art, decided the risks were worth it.

"We know that this is the right path for them: to be independent, have the chance to succeed and explore, on their own, everything the world has to offer," Aida Sandoval said when the surgery was finally complete.

Today, Erika and Eva are into typical 5-year-old stuff, Sandoval told me: They are learning numbers and love playing with kinetic sand, finger puppets and Barbie cars. The girls have also started bringing big words home from school. After a lesson about bees, they came back chattering about bee anatomy, popping out terms like "abdomen" and "thorax."

"I'm in awe at the conversations they have with me sometimes," she said.

They've made tremendous progress in their physical recovery and mobility, from sitting unassisted in early 2017, to using wheelchairs later that year, to being fitted in 2018 with custom leg prostheses.

The dynamic between them has also changed. Before separation, Eva was larger and dominated the twins' relationship. In the months after surgery, Erika's growth caught up to her sister's, and play therapy at Packard Children's helped them understand that it was OK to be separated. They have a strong sibling bond but also distinct personalities, likes and dislikes.

Both girls are getting around with a combination of prosthetic legs and walkers. The long-term goal is for them to use their prostheses with walking sticks for balance and support.

"Erika loves to get her prosthetic on and walk with us around the house," Sandoval said. "I can picture how she'll be doing it on her own as she gets older." It's a very positive change from the girls' infancy, when their parents worried that they might not be able to have independent lives.

Eva and Erika enjoy seeing photos of themselves from when they were tiny and love to hear what life was like before they were separated.

"When I see the pictures, I can't believe we were there," Sandoval said. "It still amazes me to see them at this point in their lives." — ERIN DIGITALE

VOLUME 37 NUMBER 1
ISSUE 1 / 2020

STANFORD MEDICINE

Finding a path to treating tumors
page 28

SPECIAL REPORT

Cracking cancer's code

New reasons for hope

Chemo-caused brain glitches are real
page 20

PLUS

Normal body weight can mask teen eating disorders
page 4

DEPARTMENTS

COVER: KEITH NEGLEY

letter from the dean

Our priority at Stanford Medicine is to serve our community's health needs, no matter the circumstances. Right now, as COVID-19 cases in our nation continue to rise, we are all facing extraordinarily challenging circumstances.

We are following every precaution, in partnership with the CDC and local public health officials, to protect our health care workers, our patients and the entire Stanford community.

This issue of *Stanford Medicine* magazine is about cancer, not about COVID-19. It was conceived and produced before COVID-19 became a global pandemic, and it offers some timeless perspectives. Even as our medical community responds to the immediate demands of the coronavirus outbreak, some researchers and clinicians push ahead with advances in crucial areas like cancer.

A 19th-century surgeon famously described cancer as "the emperor of all maladies," but biomedical discoveries and technological breakthroughs in the past decade give promise that the reign of this dreaded disease will soon end.

Because of the work of scientists around the globe, we have begun to see the fruits of investment in basic science research, and these advances have opened up other promising avenues of inquiry.

At Stanford Medicine, we have deployed a multifaceted approach to defeating cancer. Not only are we developing precision cures, but we are also identifying ways to predict and prevent the disease. Through this paradigm shift, which we call precision health, physicians proactively use high-tech and high-touch care to treat patients, both adults and children, holistically.

Stanford's Canary Center for Early Cancer Detection, for example, has aggressively and effectively shifted more research toward prediction and prevention. Cancers caught at stage 0 or 1 have a 5- to 10-year survival rate of 95%. Unfortunately, most cancers are caught at later stages, when survival rates plummet. By developing better diagnostics and creating more robust blood tests, we are helping to catch malignancies sooner, increasing survival rates.

The Stanford Cancer Institute, designated by the National Cancer Institute as a comprehensive cancer center, coordinates more than 450 scientists and physicians working in basic, clinical, translational and population-based science across Stanford University. Their work is advancing our understanding in diverse areas. For one, the discovery of "don't eat me" proteins used by cancer to fool the body's immune system has led to promising clinical trials. There's also the focus on using a patient's genome to identify the best possible therapy for that person. For a final example, consider the groundbreaking work at Stanford on the creation and use of human organoids to show researchers how cancer cells function and spread in human tissue.

Our research and treatment extend to survivors, who often feel adrift, unsure whether they can truly trust that cancer won't return. Our Survivorship Program aims to strengthen the community surrounding survivors to ensure they have a network that helps them navigate their new world.

I'm proud of the many ways that the care teams, researchers, students and staff at Stanford Medicine strive every day to help individuals and populations fight and beat health challenges. The knowledge gained and the efforts spent here will have a global impact — benefiting our neighbors in the Bay Area and people around the world.

Sincerely,
Lloyd Minor, MD
Carl and Elizabeth Naumann Dean of the School of Medicine
Professor of Otolaryngology-Head & Neck Surgery

GLENN MATSUMURA

upfront

A QUICK LOOK AT THE LATEST DEVELOPMENTS FROM STANFORD MEDICINE

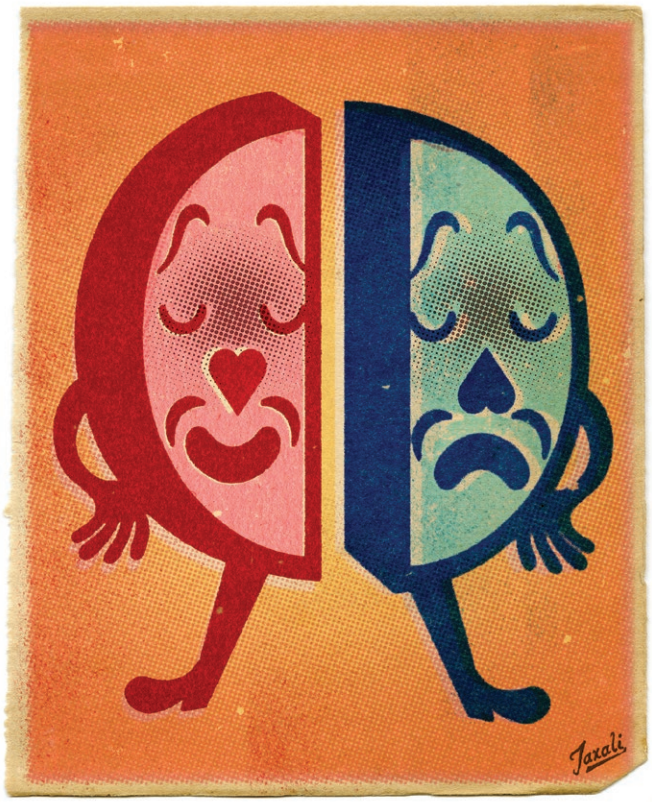
Rave new world

THE STREET DRUG ECSTASY — FORMALLY KNOWN AS 3,4-METHYLENEDIOXY-METHAMPHETAMINE, OR MDMA — gives people who take it a sense of well-being and makes them extremely sociable, even instilling feelings of unguarded empathy for strangers. It's most known for its widespread use at raves — crowded dance parties featuring electronic dance music and light shows.

If the drug's downside — its abuse potential — can be eliminated, it may also become known as a good medicine for psychiatry. In a study conducted in mice that was published Dec. 11 in *Science Translational Medicine*, anesthesiologist Boris Heifets, MD, PhD, and neuroscientist Robert Malenka, MD, PhD, appear to have succeeded in driving a wedge between MDMA's pro-social effects and its addictive properties. Heifets is the lead author and Malenka is the senior author of the study.

The researchers believe the discovery could lead to better treatments for psychiatric disorders ranging from autism to schizophrenia, which are marked by social awkwardness and withdrawal. MDMA is already in late-stage clinical trials as an adjunct to psychotherapy for post-traumatic stress disorder. Some 25 million people in the United States who suffer from PTSD could benefit from a drug capable of establishing, with a single dose in a therapist's office, a bond of trust that typically takes months or years to achieve, Heifets said.

MDMA's darker effects would be highly unlikely to occur in the one or two sessions required for patient-therapist bonding, he added.



GARY TAXALI

The death toll from the measles in the Democratic Republic of Congo has surpassed 6,000. More at stan.md/2T4QuS7.

A gift for education

JOHN ARRILLAGA, a leading Bay Area real estate developer, philanthropist and Stanford University alumnus has made a $55 million gift to the School of Medicine to eliminate medical school debt for Stanford students in need.

Stanford Medicine plans to match Arrillaga's challenge gift through philanthropic donations and increased institutional support.

The $90 million in total funding nearly doubles available assistance for students entering medical school over the next 10 years. Need will be determined by attendance cost, including tuition and living expenses, minus the available family contribution.

"This gift will be life-changing for a large number of our medical students," said Stanford President Marc Tessier-Lavigne, PhD.

New Health Trends Report

STANFORD MEDICINE'S 2020 HEALTH TRENDS REPORT released Jan. 9 showed that physicians and medical students embrace a health care future shaped and improved by technological advances, even as that same technology tests their readiness.

For the report, which focused on the rise of the data-driven physician amid a digital health care transformation, Stanford Medicine commissioned a national survey of more than 700 physicians, residents and medical students about the future of medicine and how they are preparing for it. Nearly three-quarters of the medical students and almost half the physicians surveyed are pursuing opportunities to learn new skills.

"We found that current and future physicians are not only open to new technologies but are actively seeking training in subjects such as data science to enhance care for their patients," said Lloyd Minor, MD, dean of the Stanford University School of Medicine. "We are encouraged by these findings and the opportunity they present to improve patient outcomes. At the same time, we must be clear-eyed about the challenges that may stymie progress."

Such challenges include physicians and medical students feeling ill-prepared to integrate emerging technologies into their practices and being concerned about high student-debt levels and a poor work-life balance.

"There is no better time to have a discussion about how we can prepare and support tomorrow's health care providers to rise to their fullest potential," Minor said.

Read the report at http://stan.md/2020HealthTrends.

COOLING DOWN

AS GLOBAL TEMPERATURES RISE, the average human body temperature is dipping, recent research shows.

In a study published Jan. 7 in *eLife*, senior author Julie Parsonnet, MD, professor of medicine and of health research and policy, and her colleagues reported that the average body temperature has dropped 0.05 F every decade since the 1800s.

Researchers propose that the decrease is the result of changes in the living environment, such as improvements in public health and standard of living. "Physiologically, we're just different from what we were in the past," said Parsonnet.

Hiding in plain sight

EVEN PEOPLE WHO AREN'T ESPECIALLY THIN could be suffering from anorexia nervosa, a disorder characterized by restrictive eating, overexercising, distorted body image and intense fear of weight gain. Dangerously low heart rate and blood pressure, as well as serious electrolyte imbalances and psychological problems are common among patients with the condition.

According to a new study led by researchers at Stanford and the University of California-San Francisco, teens and young adults with atypical anorexia nervosa can have normal body weights and still be dangerously ill.

Traditionally, individuals had to be below 85% of their ideal body weight to be diagnosed with anorexia nervosa. But in 2013, atypical anorexia nervosa was recognized for people who meet all other diagnostic criteria of the disorder but have a normal body weight.

"This group of patients is underrecognized and undertreated," said the study's senior author, Neville Golden, MD, professor of pediatrics at Stanford.

The research, published Nov. 5 in *Pediatrics*, showed that large, rapid weight loss is the best predictor of medical and psychological problems in atypical anorexia patients.

GARY TAXALI

Alcohol flushing tied to Alzheimer's

A COMMON MUTATION THAT CAUSES FACIAL FLUSHING and inflammation in response to alcohol can lead to biochemical changes associated with Alzheimer's disease, new research shows.

A study, conducted in human cell cultures and in mice, indicates that people with the mutation who drink alcohol could increase their risk of Alzheimer's disease, said Daria Mochly-Rosen, PhD, senior author of the research published Dec. 12 in *Acta Neuropathologica Communications*.

This mutation, which interferes with the breakdown of alcohol, is prevalent in the East Asian population. It affects about 560 million people, or about 8% of the world's population, said Mochly-Rosen, professor of chemical and systems biology.

Understanding the relationship of alcohol and genes linked to Alzheimer's disease will have broad consequences, she said, because a large group of people may unknowingly be harming their health by regularly consuming alcohol.

This mutation reduces the activity of aldehyde dehydrogenase 2, or ALDH2, which is a key enzyme for breaking down alcohol. As a result, a buildup of a toxic byproduct, acetaldehyde, causes skin flushing and inflammation — sometimes called Asian glow.

Though the new research raises the concern that alcohol drinkers with the mutation develop Alzheimer's disease at a higher-than-average rate, it's not definitive.

"Our data suggest that alcohol and Alzheimer's disease-prone genes may put humans at greater risk of Alzheimer's onset and progression," Mochly-Rosen said. "This is based on our patient-derived cell studies and our animal studies, so an epidemiological study in humans should be carried out in the future."

More research could also determine whether treatment with compounds designed to restore the enzyme's functionality reduce the progression of Alzheimer's.

Take it to heart

RESEARCHERS SAY THEY have the answer to a question that has long plagued heart doctors: What is the best treatment for patients with stable heart disease who have no chest pain? Is it medications and lifestyle advice alone, or those along with invasive surgical procedures?

The former won out, according to a study led by Stanford and New York University researchers that was announced at the American Heart Association Scientific Sessions in November.

Medications and advice — such as improving diet, exercising and not smoking — proved just as beneficial as also undergoing such invasive procedures as bypass surgery or stent implantation.

"I think these results should change clinical practice," said Stanford clinical professor David Maron, MD, co-chair of the trial. "It's hard to justify putting stents into patients who are stable and have no symptoms."

REIMAGINING SURVIVAL

BETTER CANCER DIAGNOSTICS AND TREATMENTS ARE IN THE WORKS

By Hanae Armitage and Krista Conger

ILLUSTRATIONS BY KEITH NEGLEY

CANCER IS A DISEASE OF THE AGES. FOR 4,000 YEARS, HUMANS HAVE NOTED ITS DESTRUCTIVE EFFECTS. HIPPOCRATES DUBBED THE ENEMY KARKINOS, FOR CRAB, BECAUSE CANCEROUS TUMORS ARE OFTEN FIRMLY EMBEDDED IN NORMAL TISSUE, SURROUNDED BY "LEGS" OF SNAKING BLOOD VESSELS THAT DELIVER NUTRIENTS AND OXYGEN. PERVASIVE, INVASIVE AND DEADLY, CANCER IS THE SECOND LEADING CAUSE OF DEATH IN THE UNITED STATES.

We have only recently found the means to fight back. Chemotherapy and radiation first arrived in the mid-1900s; President Nixon declared a war on cancer in 1971, establishing the National Cancer Institute and increasing research funding. We've seen a slow march forward with small but meaningful victories since. Between 1991 and 2015, overall cancer mortality dropped by 26%, primarily a result of better screening techniques that allow earlier diagnosis of cancers before they have spread to other parts of the body.

Unlike in Hippocrates' time, cancer is no longer necessarily a death sentence. On the contrary, many clinicians liken some types to more of a chronic disease similar to diabetes. Ongoing monitoring coupled with the availability of new drug

combinations can keep the disease in check for many people.

Now researchers are setting their sights on a more difficult problem — not just managing but actually curing advanced cancers. To do so, they often leverage the immune system, priming it to recognize and seek out cancer cells throughout the body by using genetically engineered CAR-T cells, for example, or by targeting tumors with agents to ramp up immune cell activity. Specially engineered antibodies are being tested in clinical trials for their ability to recognize and obscure molecules that protect cancer cells — so immune cells can gobble the cancer cells up.

They're also advancing diagnostic techniques so more cancers can be caught earlier. They're learning how to analyze minute quantities of free-floating DNA in the blood, seeking cancer indicators in the molecular backwash released when a tissue sample is blasted with a high-energy ion beam, and tweaking imaging techniques to reveal the basic details of early tumor biology.

"In biomedicine, we're faced all the time with intractable problems, and cancer is one of these problems that is very difficult to solve," said biochemistry professor Steven Artandi, MD, PhD, the Jerome and Daisy Low Gilbert Professor and the Laurie Kraus Lacob Director of the Stanford Cancer Institute. "Often these problems are solved by thinking about them in a completely different perspective, and that's the kind of attitude and approach that we foster at Stanford."

Read on to learn about some of the diagnostic tools and treatments that are on the horizon.

NEW DIAGNOSTIC TOOLS

TUMOR SCRAPS

Researchers are analyzing molecules that latch on to DNA to reveal clues about the underpinnings of cancer.

Like all tissues, tumors shed bits of themselves into the bloodstream. Cells that slough from a mass are often the first harbinger of cancerous tissue. Loose snippets of DNA also provide a wealth of information about the tumor from which they parted, sometimes down to the very mutation that caused the tumor in the first place.

These floating fragments are known as cell-free DNA, and Christina Curtis, PhD, associate professor of medicine and of genetics, is keen on understanding how they inform both ends of the cancer research spectrum — detection and treatment. The problem is that nascent tumors don't shed much DNA. Even when they do, finding rare genetic clues in a blood draw is, at best, unlikely.

Curtis and her team are taking a slightly different approach. "We're finding value in all sorts of cell-free DNA, not just that born of tumor cells," she said. "Instead of leaning solely on the genetic information found in cell-free DNA, we're looking at something called epigenomics." Roughly, epigenomics translates to "on" or "near" the genome, which makes sense — epigenomics is the study of molecules that latch on to parts of the genome to change or guide function.

Epigenomics provides a window into the molecular ecosystems of the entire body. There are millions of components in the epigenome that create patterns, revealing what's going on. For example, when someone falls ill, epigenomic molecules in immune cells begin to shift — some might latch on to the DNA while others fall off. "Blood analysis shows changes in epigenomic markers, allowing us to potentially read out things like immune activation, or inflammation," said Curtis. And because epigenomic information can come from more than just tumor cell-free DNA, it's a more plentiful data source. "We're surveying everything that's shed into the blood."

The idea is to identify patterns — epigenomic signatures — that are linked to different states of the body, including cancer. It's not the same as an official diagnosis, but the tactic would aid in early cancer detection by prompting appropriate follow-up.

Curtis also sees potential for epigenomic analysis in monitoring patient responses to immune-based cancer treatments. "We could use this approach to assess how the body is responding to new immunotherapies on a systematic level and see if the therapy is actually working," she said.

"Cancer is ever evolving, and we need to find ways to be one step ahead. It's still early days, but epigenomic changes in cell-free DNA give us another way to read that out and — hopefully — keep us one step ahead."

NOTHING WASTED

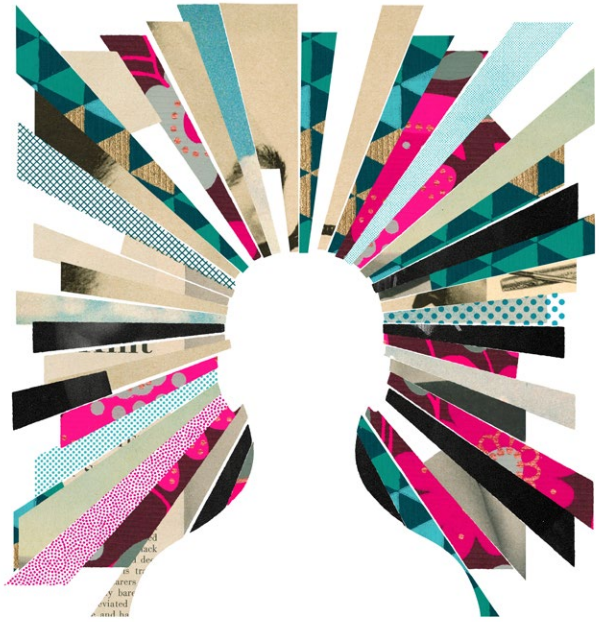
First there was the smartphone, then the smartwatch — now scientists at Stanford have created a smart toilet, detecting diseases through data that's usually discarded.

Stanford scientist Sanjiv "Sam" Gambhir, MD, PhD, has dedicated much of his career to detecting disease before it

THE BIG IDEA IS TO COLLECT, SAMPLE AND ANALYZE DATA THAT OTHERWISE HEADS STRAIGHT FOR THE SEWERS. URINE GETS ONE SET OF TESTS, STOOL ANOTHER, AND IF THE TOILET DETECTS ANYTHING SUSPICIOUS … IT SENDS AN ALERT TO THAT PERSON'S DOCTOR.

strikes. Now, he's created something that does the dirty work for him: a tech-wielding toilet that automatically monitors urine and stool for signs of disease.

Gambhir's conception of this smart toilet dates back more than 15 years. "When I told people about it, they'd laugh a little because it's kind of an odd idea," he said. Offbeat though it may be, the smart toilet is part of an arsenal of technologies Gambhir has spearheaded to detect cancer and other diseases at the earliest stage possible.



The big idea is to collect, sample and analyze data that otherwise heads straight for the sewers. Urine gets one set of tests, stool another, and if the toilet detects anything suspicious — such as blood in the urine, which can be a sign of bladder cancer — it sends an alert to that person's doctor. It even knows who's using the toilet through a couple of identification systems, such as a flush button that reads fingerprints.

Inside the smart toilet is a sort of miniature automated lab: Sensors detect whether the incoming "data" is urine or stool, allowing the toilet to execute the correct sample analysis. The appropriate disease-detecting tests are then administered, followed by one of two types of analysis: molecular, which hunts for various biomarkers; and phenotypic, which identifies physical attributes of the urine or stool, such as flow and consistency. The tests and analysis processes can even be personalized. "If you're at risk for kidney cancer, you'd likely be monitored differently than someone who's at risk for prostate cancer," said Gambhir, the Virginia and D.K. Ludwig Professor of Cancer Research.

Recently, Gambhir and his team completed the first clinical trial of the smart toilet, showing its utility in flagging suspicious biomarkers or signs of disease. The key, Gambhir said, is that the user doesn't have to do anything special. "Everyone uses the bathroom," he said. "It's the perfect way to measure health parameters without the person having to do anything differently."

Now, Gambhir and his team are revising the latest prototype into a compact accessory, fit for any toilet. "No one wants to rip out their old toilet and replace it," he said. "So we're making the 'smart' aspect of the toilet into more of a bidet-type add-on."

THE PROOF IS IN THE PARTICULATE

By shooting beams of oxygen toward tissue samples, scientists are trying to piece together an in-depth picture of cancer's molecular secrets.

Imagine a scene from a sci-fi movie where a beam of energy streams toward Earth and strikes the ground, sending a cloud of dirt and particulate matter skyward. An imaging tool devised by scientists at Stanford operates on much the same premise. It's called multiplexed ion beam imaging, or MIBI, and the burst of particulate matter in this case is used to detect and measure levels of certain molecules — such as those that flag cancer — in a cell.

"We want to get more granular by studying single cells and substructures inside those cells that could inform clinical decisions," said Sizun Jiang, PhD, a postdoctoral scholar who works with MIBI, the brainchild of immunologist Garry Nolan, PhD, the Rachford and Carlota Harris Professor, and

Michael Angelo, MD, PhD, assistant professor of pathology.

Traditional imaging techniques allow scientists to see whether immune cells have infiltrated a tumor, but MIBI, which was further developed at a company founded by Nolan and Angelo, takes it a level deeper, revealing details such as immune cell type and the specific cancer-fighting function the cell is executing.

Molecular imaging has often relied on fluorescence to label proteins and cells. But there are only so many clearly distinct hues, limiting the number of molecules for which one can search. MIBI gets around that by harnessing a tagging system that uses metals that are rare in human biology. The metals are fused to antibodies, which search for specific molecules in a tissue, such as a cancer marker. If present, the antibody latches on, acting as a flag. To detect the metal markers, the MIBI instrument shoots a beam of oxygen down into a tumor sample. Like a microscopic scene from *Independence Day*, a plume of tissue erupts, offering itself up for the MIBI detector to inspect for the presence of rare metal.

So far, the group can collect information on up to 50 distinct molecules at a time with the technology — quite a jump from the five to seven that fluorescence provides. That leap paints a more detailed image, but it also allows the researchers to begin to tease apart the molecular interactions fueling tumor formation, growth and, potentially, destruction.

"With MIBI," said Jiang, "we envision a future where clinicians and data scientists work together to attain a more complete understanding of what's going on in a tumor, and can use that information to pick the best treatment."

LIVE INTERACTIONS

Researchers are developing technology that makes short movies of cells in tumors of live animals.

A live tumor is a messy place. Cancer cells, immune cells, blood cells and others all mix together, sending and responding to a frenzy of signaling that often represents opposing forces — either aiming to help or hinder tumor growth.

Cancer researchers want to know what those cells are doing and how they interact, but it's not easily deciphered, especially from a still image or slice of tissue.

"What's been missing from fundamental cancer biology research is a way to actually see the conversations and interactions between cells," said Adam de la Zerda, PhD, associate professor of structural biology.

He has built on a technology, called optical coherence tomography or OCT, to fill that niche. The noninvasive imaging technique, often used to inspect the retina during eye exams, offers an expanded window into the world of living tissues, including tumors. De la Zerda has added a twist to the long-established imaging method using gold nanoparticles that, when pooled in a tumor, refract light in a way that enhances detail in the OCT scan.

De la Zerda's technique doesn't sleuth out signs of cancer, so it isn't a tool for early cancer detection — but it could shed light on a host of molecular details that better inform cancer diagnosis overall. By fusing gold particles to antibodies, the particles can even be sent to a particular cell or protein: An antibody will shepherd the gold particle to a specific molecular structure in the body, such as a cancer marker.

"For the first time, we're able to actually see the cells traveling around in the tumor, where they go or don't go, and the other cells they're interacting with," said de la Zerda. The method has been used only in mice, but one day could be used to show how immune cells infiltrate a tumor, informing which treatments work best for specific patients.

The gold nanoparticles are not approved for use in humans, but that's the goal. The amount needed to visualize a tumor's specifics is minuscule — "less than what's consumed in a gold leaf on a fancy chocolate cake," said de la Zerda.

"We've known that there are lymphatic vessels in tumors, but for the first time we've been able to show that these vessels are performing a duty and draining the tumors of fluid," he said. "For us, it's akin to the difference between finding evidence of water on Mars and actually finding water on Mars."

NEW TREATMENTS

FIGHTING THE UNKNOWN

Priming the immune system to hunt for cancer throughout the body might eliminate distant metastases and future recurrence.

Vaccinating against cancer may seem too good to be true. In fact, the approach developed by professor of oncology Ronald Levy, MD, isn't what most of us would think of as a vaccination. Unlike a classical vaccination, which prevents disease before it starts, this one bolsters the body's battle against disease that already has a foothold. Levy, who has dedicated his career to fighting blood cancers, injects existing tumors with an agent that gives an activity boost to immune cells called T cells that have infiltrated the cancer and begun to fight it. Often, however, these cells become exhausted in their

efforts and tamp down their cancer-fighting activity.

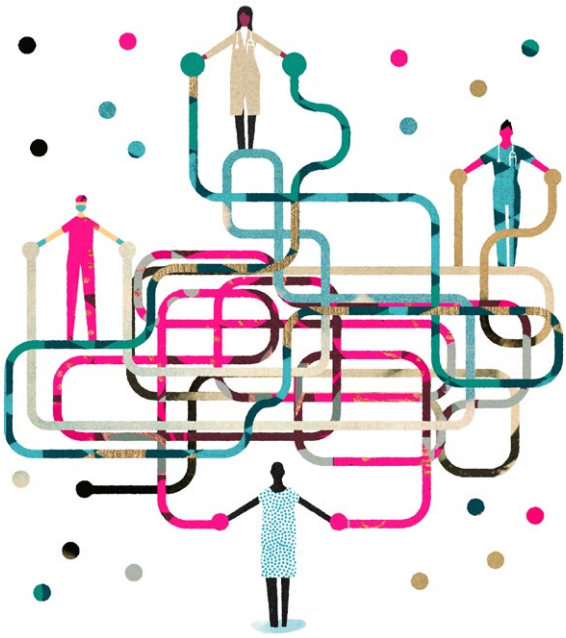
In early 2018, Levy and his colleagues, including instructor of medicine Idit Sagiv-Barfi, PhD, showed that this strategy could eliminate established human tumors in mice not only at the site of injection but also at distant sites throughout the body. The newly reactivated, unleashed T cells could also prevent the future development of mammary tumors in a mouse model of breast cancer.

Since the original mouse study, Levy has launched a series of trials to test the safety and efficacy of the approach in humans. So far the treatment seems safe in humans, and there are hints it may also be effective. Of 29 people with lymphoma enrolled in the initial trial, nearly all saw their tumors at the treated site shrink. Furthermore, 24 also experienced a reduction in tumor volume at distant, untreated sites.

"We're very encouraged," said Levy, noting that many other trials around the country are employing variations on the technique. "Our goal is to amplify an immune response that already exists in and around the cancer and use that to fight cancer throughout the body."

Levy is currently leading three additional trials of the technique — two in patients with lymphoma and one in patients with any type of advanced cancer. He envisions that the approach could be used in combination with surgery or other types of drug therapy.

"This could be a new way of approaching the initial treatment of cancer," said Levy, the Robert K. and Helen K. Summy Professor of the School of Medicine. "We could treat tumors before surgery to get the immune system to fight small metastases elsewhere in the body we don't even know of at the time. Theoretically this could be used whenever there is a tumor that we can inject."



IN A FLASH

Rapid, high-power radiation may eliminate cancers in an instant with less damage to healthy tissue.

Stop. Hold as still as you can. Don't move a muscle.

It's harder than you think. Now imagine that your ability to remain immobile is vital to the effectiveness of your cancer treatment.

That's the situation for patients undergoing radiation to zap tumor cells. Despite the best efforts of patients and their clinicians, there are still variables that can't be controlled. Your heart will still beat, your intestines will still contract and blood will still pulse through your body.

Radiation oncologists have tried to counter this movement by immobilizing the patient with temporary restraints and delivering the dose as quickly as possible. But new technology may make such concerns a thing of the past. Researchers at Stanford Medicine, including professor of radiation oncology Billy Loo Jr., MD, PhD, and at Stanford's SLAC National Accelerator Laboratory have devised a linear accelerator capable of rapidly delivering high doses of radiation. The accelerator is known as PHASER (for pluridirectional high-energy agile scanning electron radiotherapy) and the act of delivering the radiation quickly is called FLASH. Together they are likely to shake up the field of radiation oncology.

"The delivery of radiation by PHASER is nearly instant," Loo said. "Currently, a single high dose of radiation takes about three minutes to deliver; it can take up to 30 minutes for very complex cases. In contrast, the PHASER technology can deliver the same dose in a fraction of a second."

Because there's little time for the target area to move

'WE'RE VERY ENCOURAGED. OUR GOAL IS TO AMPLIFY AN IMMUNE RESPONSE THAT ALREADY EXISTS IN AND AROUND THE CANCER AND USE THAT TO FIGHT CANCER THROUGHOUT THE BODY.'

around, the delivery of the radiation is much more precise than current methods.

There's another bonus. "No one expected that delivering the radiation much faster would also reduce the damage to normal tissue," Loo said. "But surprisingly we are seeing much less collateral damage to normal tissues and organs, without reducing the ability to kill tumors."

In 2019, Loo and his colleagues showed that mice whose brains have been irradiated with the new rapid technique experienced fewer cognitive problems than mice that received the same dose of standard radiation.

"In many cases we couldn't tell the difference between mice irradiated with FLASH and the un-irradiated controls," Loo said. "Anything we can do to reduce radiation damage in humans, particularly in children whose brains are still developing, would be a big win."

EASY DOES IT

Gentler pretreatment could vastly expand who could benefit from stem cell transplants.

Blood cancers like leukemia or lymphoma arise when blood cells run amok in the body, dividing unchecked and crowding out other important cells of the blood and immune system. For many years, the last-ditch measure to cure these conditions was a hematopoietic stem cell transplant (previously known as a bone marrow transplant). But before healthy cells can be infused, the diseased cells in the bone marrow, where all blood cells originate, must be eliminated.

Until recently, this wholesale elimination of a patient's blood system was accomplished through a devastating combination of chemotherapy and radiation that kills the cells in the marrow. Although effective, the treatment, known as conditioning, is brutal for patients. For some, like the elderly, the very young or very sick, it's not even an option.

Could there be a better way? A series of ongoing Stanford studies suggests so.

The studies build upon discoveries in mice made by Agnieszka Czechowicz, MD, PhD, now assistant professor of pediatrics, and Irving Weissman, MD, professor of pathology and director of the Institute for Stem Cell Biology and Regenerative Medicine, that showed that conditioning can instead be done with antibodies that recognize and block the activity of a critical survival protein called CD117 on the surface of blood stem cells. This allowed transplanted donor blood stem cells to engraft with subsequent replacement of the blood and immune system without toxicity.

Under the leadership of Judith Shizuru, MD, PhD, a professor of medicine and pediatrics, and Maria Grazia Roncarolo, MD, the George D. Smith Professor in Stem Cell and Regenerative Medicine, this work is being translated from mice to humans in a clinical trial in children with the rare, fatal genetic disease called severe combined immunodeficiency, also known as "Bubble Boy Disease."

Subsequent studies by the Stanford researchers have shown that blood stem cells can be eliminated even more effectively with a combination of antibodies against both CD117 and CD47 (a protein expressed by many cancer cells) or by attaching a cell-killing drug to CD117 antibodies. These approaches, in tandem with a cocktail of immune-suppressing antibodies, can even allow mice to accept immunologically mismatched hematopoietic stem cells and tissues.

The findings, which have sparked multiple additional clinical trials, are likely to transform the way hematopoietic stem cell transplants are performed, vastly broadening the pool of patients who could benefit and the range of blood and immune diseases that could be cured by such therapies.

TO EAT OR NOT TO EAT

Unleashing immune cells to gobble cancers helps the body fight back.

Macrophages are often the unsung heroes of the immune system. They're not glamorous like T cells, those highly selective assassins that target specific antigens on the surface of sick cells or microbial invaders. Or like B cells, which, when triggered, churn out millions of similarly specific antibodies to course through our bloodstream and lymphatic system to tag cells for destruction.

Instead, macrophages are part of what's known as our innate immune system — the infantry that does a lot of the grunt work. Macrophages constantly patrol the body looking for signs that something is amiss. When they recognize a sick or dying cell or a foreign invader, they glom on to and engulf the target like an amoeba with a hapless bacteria snack. They then send out signals to alert T cells to the presence of trouble.

Despite the seeming drudgery of their job, macrophages are increasingly recognized as key players in the development of new immunotherapies. Their post on the immunological front line has brought them to the attention of cancer researchers that include Weissman, the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research.

In 2009, Weissman's lab identified the CD47 protein, which is found on the surface of nearly every human cancer

FROM CARE TO CURE

STANFORD CANCER INSTITUTE IS STRIVING TO CHANGE THE STORY FOR PEOPLE WITH CANCER

If two heads are better than one when it comes to problem solving, it stands to reason that hundreds of the best and brightest minds can accomplish great things. The Stanford Cancer Institute brings together over 400 faculty members from four schools and more than 30 departments in a collaborative, interdisciplinary effort to improve the diagnosis, treatment and prevention of cancer.

These physicians, basic and translational researchers, clinical trial experts and population scientists are developing novel prevention and detection strategies and creating and delivering innovative therapies from immunotherapy to new, targeted drug treatments for many types of cancer. More than 250 cancer clinical trials are recruiting people from California and beyond.

The institute holds an annual comprehensive cancer research training program, and it oversees doctoral programs in cancer biology, as well as the education and training of the next generation of clinician researchers. The institute also is developing a research program in cancer engineering, and recently invested in the new Department of Epidemiology and Population Health.

In 2016, the National Cancer Institute designated the Stanford Cancer Institute a Comprehensive Cancer Center — an elite status earned through a competitive review process by institutions demonstrating an integrated, wide range of cancer research spanning from basic laboratory research to translational, clinical and population-based sciences.

These efforts mean researchers are poised to supplement stellar cancer care with advanced cancer treatments. "This is an incredibly opportune time," said the institute's director Steven Artandi, MD, PhD.

studied. CD47 is recognized by a receptor on the surface of macrophages and serves as a "don't eat me" signal that stops macrophages in their tracks. Blocking this binding with an anti-CD47 antibody releases the brakes on macrophage activity and, in mice, led to the elimination of many human cancers.

Now Weissman and his colleagues, including hematologist Ravi Majeti, MD, PhD, and oncologist Branimir Sikic, MD, who are both professors of medicine, and the company Forty Seven Inc., are conducting early-phase clinical trials of the antibody (in combination with immunotherapy drug rituximab) in people with a variety of cancers.

Results from the first trial, which enrolled 22 people with lymphoma, showed the treatment was well tolerated; some patients saw disease regression. In a second phase-1 trial of 62 people with advanced solid cancers, the treatment was also well tolerated; two people experienced partial remissions. Seven trials are ongoing of the antibody, known as magrolimab, either alone or in combination with other immunotherapies or chemotherapies. Some of these trials have shown promising results in patients with myelodysplastic syndrome and elderly patients with acute myelogenous leukemia.

AT A CRITICAL POINT

From new imaging techniques to revved-up immune systems, it's apparent that we're on the verge of making big strides in cancer diagnosis and treatment.

Recently, the American Cancer Society announced that the United States experienced its single biggest drop ever in cancer mortality in 2017.

In particular, deaths from lung cancer and melanoma have declined significantly — a fact hailed by National Cancer Institute Director Norman Sharpless, MD, in a recent talk at Stanford.

"When you have an effective therapy, added to good prevention and good screening, you can really make a difference in these cancers," Sharpless said.

"We are at a critical point in the history of cancer now," said Artandi, the Stanford Cancer Institute's director. "Over the next five years we need to continue with fundamental basic science discoveries in cancer, while translating these findings to our cancer patients by expanding and accelerating our clinical trials. This pipeline bringing new drugs and other therapies to our cancer patients is an essential step in curing patients with cancer." SM

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fledging – with cancer

HELPING TEENS AND YOUNG ADULTS NAVIGATE CARE AND RECOVERY

By Erin Digitale

PHOTOGRAPHY BY TIMOTHY ARCHIBALD

One day in June 2014 after 17-year-old David Llano had a routine physical, his doctor told him he needed extra blood work. The Sunnyvale, California, teen wasn't worried; he felt great. School had already let out for the year and he'd been playing basketball with his buddies the day before.

But the tests that Llano ultimately had at Stanford showed that he had a form of blood cancer called acute myeloid leukemia. His bone marrow was packed with malignant cells, rendering his blood-clotting and immune systems nonfunctional.

Instead of spending the summer before his senior year of high school hanging out with his friends and his twin sister, Emma, he was hospitalized immediately to begin what was expected to be a minimum of several months of intense treatment.

"I was shocked, I was out of words, I was sad," Llano, now 23, said recently. "All the emotions you would think I felt, I felt."

There's no good time to have cancer, but the teen and young-adult years are especially hard. Starting in the early 2000s, oncologists recognized that, compared with younger children or older adults, cancer patients in this group are especially vulnerable and are less likely to be cured, not only because of their biology but also because of emotional and social factors.

Ever since, experts have been researching the needs of young cancer patients and the barriers they face to treatment. Their conclusions — which range from offering more

AFTER A MONTHSLONG BATTLE AT AGE 17 WITH ACUTE MYELOID LEUKEMIA, DAVID LLANO, NOW 23, DECIDED TO PURSUE A CAREER AS A CHILD-LIFE SPECIALIST HELPING TEENS COPE WITH CANCER.

clinical trials to helping patients salvage elements of normal adolescence — are driving big shifts in cancer care for young people.

UNIQUE CHALLENGES OF YOUNG PATIENTS

MORE THAN A DECADE before Llano's diagnosis, oncologists attending the 2000 meeting of the American Society of Hematology got their own bad news. At the time, cancer patients on the edge of adulthood weren't treated uniformly; they might have received pediatric care if they lived near a children's hospital, but health insurance providers also often assigned them to oncologists who worked with adults. At the scientific meeting, researchers reported that 18- to 20-year-olds with a common blood cancer, acute lymphoblastic leukemia, had vastly different outcomes when they received treatments developed for adults instead of those for children.

For this specific disease and specific age group, pediatric and adult treatments were equally likely to get rid of cancer, achieving complete remission for 90% of patients. But those treated with pediatric protocols were about twice as likely to remain cancer-free seven years later.

"It shook people up," said Gary Dahl, MD, professor of pediatrics and an oncologist at Lucile Packard Children's Hospital Stanford.

One reason for the difference was that pediatric oncologists gave stronger chemotherapy, including a drug called asparaginase, to their leukemia patients.

Children with cancer often receive more powerful chemo than adults, in part because they are better able to recover from strong, high-dose chemotherapy. Pediatric oncologists have figured out how to provide supportive care for the drugs' side effects. Also, doctors try to use less radiation in children to reduce the risk of secondary cancers and compensate with stronger chemo treatments.

Subsequent evidence showed that teen and young-adult cancer patients were universally vulnerable. A 2006 report from the National Cancer Institute and the National Institutes of Health, for instance, showed that for cancer diagnoses in patients aged 15 to 39, survival rates were improving more slowly than for older or younger patients.

"We realized the disease is different, the patient is different, and we need to find different ways of understanding that and helping address it," said hematologist Michaela Liedtke, MD, associate professor of medicine, who treats young-adult blood cancer patients at Stanford Health Care.

A FAMILY LEARNING TO COPE

FOR LLANO'S MOM, Mónica Hennings, his diagnosis felt real — in a terrible way — when Llano checked in at Packard Children's and she first saw the word cancer above the door of the Bass Center for Childhood Cancer and Blood Diseases. "It really targeted me," Hennings said.

She and her husband, also named David Llano, had already lost a child to cancer: The twins' younger brother, Gabriel, died of a brain tumor at age 2 in 2001. After his death, the family moved from their home country of Peru to California. Two weeks into her older son's treatment, Hennings quit her job as a nanny so she could care for him.

In the hospital, the teenage Llano started chemotherapy.

"When you're in the hospital room — and I did this for, like, the first three weeks of treatment — you just pity yourself, you just feel bad," he said.

He was lonely, and felt devastated when his hair fell out. He soon decided to delete his social-media accounts. "Seeing other people, your friends, around the same age as you, having normal, healthy lives, and you're just in a hospital room, it's pretty sad," he said.

Slowly, Llano figured out how to cope with his new existence. His caregivers connected him with another teen who was further along in his treatment. And Llano began venturing out of his room, talking to nurses and other patients. The hospital's child-life specialists helped him find ways to feel like himself, and he realized that making friends inside the hospital was essential. "I'm a very social guy; that's always who I've been," he said. "I wasn't going to change because I was sick."

Unfortunately, his first round of chemotherapy failed. By mid-July, when his doctors hoped he'd be in remission, 82% of the cells in his bone marrow were still malignant. (The threshold for remission is 5%.) Llano also had several infections — a common problem for blood cancer patients — and ended up moving back and forth between home and the hospital for a few months.

FACING ADULT DECISIONS

PEDIATRIC CANCERS have become more curable in the past 40 years because most young children with cancer enroll in clinical trials, giving them access to new therapies while also advancing the field. But teens and young adults often miss these opportunities. "They're too old for pediatric trials, and they may not qualify for an adult trial," said Liedtke.

Historically, the upper age limit for pediatric cancer trials was around 18, while many adult trials didn't admit patients younger than 30. Although this has been rectified, it's not the only issue. Doctors might also fail at explaining the value of clinical trials to young adults, Liedtke said. "Usually, someone older has more of a concept of what a clinical trial means, and an adolescent or young adult may think, 'I'm not familiar with this, so why would I participate?'"

Newer trials are addressing the unique biological and medical issues that arise in treating teens and young adults. For instance, asparaginase, once thought too strong for adults, has been shown to benefit leukemia patients up to age 29. Many trials are also testing how to help young patients manage the social and emotional aspects of having cancer.

Even when evidence for treatment is excellent, teens and young adults might struggle to follow their chemotherapy regimens, discounting the consequences of missing their medications.

"They may think, 'This pill makes me feel horrible; I'm not going to take it anymore,'" Liedtke said. In the 2000s and 2010s, Stanford professor of psychology Brian Knutson, PhD, and colleagues worked with a San Francisco-based organization, Hopelab, to develop a video game called *Re-Mission* that educates teen cancer patients about their treatment. "We ran several studies that proved that kids who played the video game took their meds more consistently," Dahl said.

Another key step in helping these patients came in 2015 with the founding of the Stanford Adolescent and Young Adult Cancer Program, which serves patients at Stanford's pediatric and adult cancer centers. The program aims to ensure that all aspects of a patient's needs are met, bringing oncologists together with experts in psychology and psychiatry, pain management, recreational therapy, fertility and reproductive health, and palliative care. But it also depends on input from patients.

"The patients teach me something new about this population every day," said program director Pamela Simon, a nurse practitioner at Packard Children's. Simon meets regularly with an advisory council of current and former young cancer patients who offer a perspective that the oncology doctors and nurses can't. "We have to help support these patients to be able to tell their stories."

To help childhood cancer survivors navigate the transition to adulthood, Packard Children's and Stanford Health Care oncology experts plan to launch a one-stop medical clinic in the Stanford Cancer Center this year.

'USUALLY, SOMEONE OLDER HAS MORE OF A CONCEPT OF WHAT A CLINICAL TRIAL MEANS, AND AN ADOLESCENT OR YOUNG ADULT MAY THINK, "I'M NOT FAMILIAR WITH THIS, SO WHY WOULD I PARTICIPATE?"'

NAVIGATING SHIFTING PRIORITIES

After Llano's first round of chemo failed, his medical team had no obvious path forward. "He wasn't eligible for any studies," said his oncologist, Norman Lacayo, MD, associate professor of pediatrics. "We had to be creative."

So Lacayo and his colleagues chose three drugs intended to broadly, randomly change the packaging and regulation of Llano's cancer cells' DNA. Although in an early trial these drugs were found to be ineffective in children, they often worked in adults. After that, Llano received chemotherapy intended for a different leukemia diagnosis, an approach that sometimes works because leukemia cells can have mixed phenotypes that make them vulnerable to more than one drug regimen.

Llano and his mom approached treatment as a team. "We split the responsibilities in a very nice way," Hennings said. They agreed that he would take care of the chemotherapy port implanted in his chest and she'd track the timing and dosing of his medications when he wasn't hospitalized.

Although Llano said his illness brought him and his parents closer, it's not uncommon for cancer to strain teen patients' relationships with their parents.

"You're in the process of launching and then this, like a bungee cord, pulls you back into functioning in a much younger role because you need to be taken care of," said psychologist Emily Ach, PhD, clinical assistant professor of psychiatry and behavioral sciences, who works with Packard Children's cancer patients.

Ach educates parents about how to balance a teen's needs for support, both medical and psychological, with their own worries. "It's helping parents understand what their child is most focused on, which might be, 'What are my friends going to say if they see I have no hair?' Meanwhile, the parent is thinking, 'Is my child going to survive?'"

Giving teens meaningful input into their care requires parents to cede some control, said Simon. Before patients turn 18, their parents have the final say, legally, in cancer treatment decisions. But teens need opportunities to weigh in, to talk to their doctors and ask questions without their parents around, as is standard practice in other adolescent medicine specialties. "Cancer makes it much more difficult because a parent may say, 'I might miss something really important,' " Simon said.

DECIDING ON A TRANSPLANT

THE FIRST REALLY good news came for Llano's family by mid-August: His new chemotherapy had worked and he was in remission.

However, his medical team explained, the leukemia was extremely likely to relapse. To prevent this, Llano needed a stem-cell transplant to replace his blood-forming stem cells with a donor's. The physicians also explained the risks of the procedure, such as graft-versus-host disease, in which the new immune cells from the donor attack the recipient's body.

Fortunately, his twin sister was immunologically matched and was able to donate bone marrow.

To Llano, going ahead with transplant seemed like an obvious choice. He remembers thinking of the months of illness he'd endured, and he didn't want to go through that again.

"It was his decision," Hennings said, though she was daunted by possible complications. "I was really scared when he decided to do it."

Lacayo recalled how Llano handled the situation. "He was very vocal, very grateful, and said, 'Of course I want to go to the next step.' Some of the older teens we take care of defer to their parents, but he was upfront about saying, 'Yes, I want a transplant.'

"I can't tell you for sure, because I've never talked with David about this, but he may have wanted to comfort and care for his parents because they had already lost a child to cancer."

'HE WAS VERY VOCAL, VERY GRATEFUL, AND SAID, "OF COURSE I WANT TO GO TO THE NEXT STEP." SOME OF THE OLDER TEENS WE TAKE CARE OF DEFER TO THEIR PARENTS, BUT HE WAS UPFRONT ABOUT SAYING, "YES, I WANT A TRANSPLANT." '

EASING INTO A NEW REALITY

LLANO RECEIVED stem cells from his sister on Sept. 23, 2014. For the next few weeks, he had virtually no immune system and was confined to his hospital room to give the transplanted cells time to establish themselves in his body.

He was so ill he usually didn't know what day it was and felt extremely isolated. His parents took turns staying overnight in his room. And his sister, who was in the process of touring colleges, sometimes worked on her applications while visiting him. Though Llano aimed to finish high school on time, he had trouble seeing further into the future. "You don't really have an identity," he said. "You're like, 'I have cancer and I'm trying to figure out who I am.' "

New facilities at Packard Children's have

eased the kinds of challenges Llano faced. In late 2019, the pediatric cancer center's inpatient unit moved into the fifth floor of the hospital's main building, a long-planned step for the hospital. The entire stem-cell transplant unit of the center has a positive-pressure ventilation system to keep its air extremely clean. Instead of being stuck in their rooms during the riskiest phase of the transplant process, patients can spend time anywhere in the unit. They also need to wear only a face mask when they leave their rooms, rather than head-to-toe protective gear.

AFTER DAVID LLANO WAS DIAGNOSED WITH ACUTE MYELOID LEUKEMIA, HIS MOTHER, MÓNICA HENNINGS, RIGHT, QUIT HER JOB TO CARE FOR HIM, AND HIS TWIN SISTER, EMMA, DONATED BONE MARROW FOR HIS STEM CELL TRANSPLANT.

"That's a big deal for teenagers, to be able to wear their own clothes," said oncology nurse Kim Williams, the new unit's patient-care manager. "In terms of patient outcomes, the evidence supports being up, being able to socialize, to ambulate and to have a treatment plan that includes all of that."

LOOKING AHEAD AND FINDING A PASSION

In mid-October, Lacayo gave Llano more good news: The transplanted stem cells had engrafted, giving him a healthy, new, cancer-free immune system. Llano was still dealing with aftereffects of his treatment, including mild graft-versus-host disease that affected his skin, and neuropathy that left one foot numb and difficult to move. But he could rejoin his classmates for his senior year of high school.

The first day back at school was harder — weirder, really — than he expected.

"People I didn't even know would go up to me and hug me, be really touchy with me," he said. "All the kids pitied me."

His experience isn't unusual, psychologist Ach said. "Maybe at college reentry, kids are more sensitive and appropriate, but not necessarily," she said. "In high school, they're pretty reliably not, and being different in any way is really hard."

Ach hopes to expand therapy options to help teens and young adults navigate the transition back to their regular lives after treatment. It's common for them to struggle with the distance that their cancer experience opens between them and their friends.

"They see their friends pissed off that 'Mom wouldn't let me go to that party,' and they think, 'I've got bigger things to worry about.' It kind of drives a wedge between their perspective and what's important to their peers."

To avoid unwanted attention, Llano decided to complete his senior year at the hospital school at Packard Children's. His mom drove him there each day.

He also had physical therapy to regain the use of his numb foot. But his energy was limited. He stayed close to a few friends who hung out with him at his family's home, and he increasingly drew support from friends he made at the hospital.

Gradually, he also realized that he wanted to help other teens going through cancer. In 2015, when the adolescent and young adult cancer program launched, Llano and his mother accepted an invitation to join the patient advisory council.

In addition, Llano participated in peer-to-peer counseling with other patients. Although some of the patients he met died of their disease, he wasn't deterred. Instead, he set his sights on becoming a child-life specialist and began investigating what education he'd need to make that happen.

"Looking back at it, I feel like I did figure out who I was," Llano said. He's now a junior at California State University, Long Beach, earning a bachelor's in human development and planning for the next steps of his child-life training. "I think I grew up as a person when I was in the hospital." SM

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MIND JUMBLE

UNDERSTANDING CHEMO BRAIN

By Ruthann Richter

ILLUSTRATION BY GÉRARD DUBOIS

SARAH LIU WAS TREATED FOR LEUKEMIA AS A TEENAGER. SHE ATTENDED HER HIGH SCHOOL GRADUATION ON A FOUR-HOUR PASS FROM LUCILE PACKARD CHILDREN'S HOSPITAL STANFORD AND WAS BALD UNDER HER WHITE GRADUATION CAP, HER ARM BANDAGED WHERE SHE'D BEEN RECEIVING CHEMOTHERAPY DRUGS.

Liu survived cancer and the ordeal of her treatment, and for many years she thrived. But today, at 53, she struggles to remember the names of all the Stanford oncologists who helped her, though she reveres them for saving her life. Many years later, her childhood cancer treatments — chemotherapy and radiation — have left her brain muddled.

She sometimes blanks out in the middle of a conversation or while reading a paragraph; her brain just shuts down, she said. When her brain tires, she can't focus on the task at hand and is unable to follow a narrative, whether it's in a book or on a television show. And she frequently forgets things. Liu said she is grateful to have survived, but her survival has come at a great cost.

"I think it's a complete myth that you live past the five-year survival rate and that's it, you're clear. For pediatric cancers in particular, that's not true. These drugs and radiation all have a profound effect," said Liu, a Berkeley, California, resident.

"You survive, but the price you pay to survive can be very traumatic."

She's among the legions of cancer survivors suffering from chemo brain, a neurological disorder formally known as chemotherapy-related cognitive impairment. The majority of patients who overcome cancer experience the condition, which is marked by mental fogginess, slowed thinking, memory problems, inability to multitask and sometimes anxiety, said neuro-oncologist Michelle Monje, MD, PhD, an associate professor of neurology and neurological sciences at Stanford. The symptoms may show up during treatment or months later. There is no cure, though some medications may help minimize symptoms, said Monje, who advises patients to consult with a neurologist familiar with the condition. She said there is also some evidence that aerobic exercise improves cognitive abilities after cancer therapy.

MICHELLE MONJE
Monje is one of a small group of scientists exploring the biology of cancer therapy-related cognitive impairment.

"Cancer is not done when the cancer is gone," Monje said. "We need to follow up on the pretty serious consequences of these life-saving therapies and hopefully promote regeneration and healing of the damage done by these very powerful treatments."

For the past two decades, Monje has studied cancer therapy-related cognitive impairment along with a small community of neuroscientists across the country who are excavating the biology that underlies the disorder. Two of the major cancer treatments, radiation and chemotherapy, can lead to cognitive difficulties, though the impacts of cranial radiation tend to be more severe and to progress more rapidly. Scientists have recognized the effects of radiation on the brain for decades, but they have only recently begun to appreciate the true impact of chemotherapy on the brain.

Monje's latest studies, published in 2018 in *Cell* and last year in *Neuron*, have uncovered a cascade of cellular events caused by the common chemotherapy drug methotrexate that can disrupt brain function and cognitive abilities. Moreover, she and her colleagues have identified two molecules that can forestall the damage and restore normal brain processing, at least in mice.

"You never know what happens going from mouse to humans. However, we are encouraged that these drugs have worked in a number of entirely different mouse diseases," said Frank Longo, MD, PhD, professor and chair of neurology at Stanford who has collaborated with Monje. "We think we are really targeting a fundamental mechanism. It gives us a little more hope that the effects we're seeing in mice might also occur in humans."

Monje said she thinks of chemo brain as "plasticity interrupted," a glitch in the brain's ability to change and adapt.

"I think it can be reversed," she said. "I'm very hopeful that we'll be able to truly treat and repair the damage caused by our necessary but toxic cancer therapies."

Some 15.5 million Americans have survived cancer, and the number is expected to grow to 20 million by 2026, according to the National Cancer Institute. It's estimated that at least half of these individuals may suffer long-term effects from treatment that can hinder their ability to work, succeed in school and perform daily tasks, Monje said.

SYMPTOMS 'ROB' PATIENTS' SOUL

Stanford pediatric oncologist Paul Fisher, MD, recalled one patient who became distraught because she was having trouble finding her way in her neighborhood seven years after being treated for brain cancer. He was empathetic, but couldn't offer a remedy.

"She was driving her child to school and got lost. She was just beside herself," said Fisher, the Beirne Family Professor of Pediatric Neuro-Oncology.

"What's most gripping is when people are cognizant enough, like she was, to know they aren't the person they were — they are aware that they have deficits.

"Thinking, talking, memory — that's who you are," he said. "That's the very part of your soul. That's the thing that is devastating to people. It robs their soul."

TIMOTHY ARCHIBALD

Some studies of women with breast cancer show that, even 20 years later, some have such serious cognitive problems that they are unable to return to their jobs and regain the level of function they had before therapy, Monje said. In children with cancer, the long-term effects are even more profound because the drugs assault the brain during a key time in development, she said. These children may not be able to finish college or live independently, particularly if they've had radiation therapy to the brain, she said.

"They may never drive a car. They may never get married. This really alters lives," said Monje, whose clinic is focused on treating children with brain tumors. "Of course, it's a spectrum, as some do better than others. I certainly know MD and PhD students who were treated for cancer in childhood. There are many variables. But it's a big problem."

Monje's interest in the condition was sparked in 2000, when she was a Stanford medical student. In treating cancer patients, she was disturbed to see so many suffering from negative long-term neurologic consequences, particularly those who'd had radiation therapy. She went on to complete her PhD in neuroscience at Stanford, where she teamed up with Theo Palmer, PhD, a professor of neurosurgery, to examine how radiation therapy affects the hippocampus, an area of the brain central to forming memories and one of the few areas in which new neurons are formed throughout life.

To their surprise, the researchers found that radiation to the brain in laboratory mice caused harm by revving up the microglia — immune cells in the brain that surround neurons. The microglia were causing inflammation, which prevented new neurons from forming. When the mice were given the common anti-inflammatory drug indomethacin, it reversed the harm and restored normal brain function, the scientists reported in 2003 in the journal *Science*. As a consequence of these findings, clinicians now shield the patient's hippocampus during radiation therapy.

"Now it's very well established that microglia play fascinating and diverse roles in nervous system development and disease," Monje said. "But at the time, the idea of microglia influencing the development of neurons — wow, that was unexpected." It was also a hint of things to come.

CONFIRMING CHEMO BRAIN'S VALIDITY

One of Monje's colleagues during her residency at the Harvard-affiliated Massachusetts General Hospital, Jorg Dietrich, MD, PhD, conducted early studies of chemo brain. In one published in 2006, his team tested three common chemotherapy drugs and analyzed their effects side by side on human cancer cells in the lab and normal brain cells, and found the drugs were more lethal to brain cells than to the cancer cells. Their work also showed that the immature cells of the brain, progenitor cells, which are crucial for maintaining brain plasticity throughout life, were particularly vulnerable to chemotherapy.

'CANCER IS NOT DONE WHEN THE CANCER IS GONE. WE NEED TO FOLLOW UP ON THE PRETTY SERIOUS CONSEQUENCES OF THESE LIFE-SAVING THERAPIES AND HOPEFULLY PROMOTE REGENERATION AND HEALING OF THE DAMAGE DONE BY THESE VERY POWERFUL TREATMENTS.'

The finding ran counter to what clinicians had long maintained — that the mental fog following cancer treatment was just a sign that patients were depressed about their disease, Dietrich said.

"We really had to work against this dogma in the field for about 20 years," said Dietrich, a professor of neurology at Harvard who directs a clinic focused on the neurologic effects of chemotherapy and radiation. Because no one wanted to believe that drugs targeting cancers outside the central nervous system could penetrate the blood-brain barrier and harm brain cells, the oncology community continually pushed back on this body of research.

"I think there was just enormous anxiety in the field of oncologists and providers that there was the risk for damage to

the brain, but they didn't want to acknowledge this because there really wasn't any alternative," he said.

He said the ground began to shift around 10 years ago when evidence piled up confirming that cancer drugs could in fact target the brain and harm the brain's support system — the glial cells, which nourish and protect neurons and make up about half of the cells in the brain and spinal cord. Glial cells include not only the microglia but also astrocytes — star-shaped cells that help neurons get nutrients and maintain their connections to other cells — and oligodendrocytes, which help build myelin, the protective sheath that insulates brain cells and allows for fast transmission of signals between them. Without myelin, signals become slowed or confused.

Recently, Monje's lab completed research in laboratory mice that shows how the cancer drug methotrexate disrupts these three types of glial cells. In one study, her team found the drug first activated the microglia to cause inflammation. That provoked a reaction from astrocytes. That, in turn, disrupted the formation of oligodendrocytes. The mice in the study reacted by moving slowly and showing signs of anxiety, impaired attention and memory problems. These changes persisted for at least six months after the animals were given methotrexate, a long time in the life of a mouse.

Most importantly, the researchers found that when they gave the animals a compound that depleted the microglia, an experimental drug called Plexxikon 5622, it corrected the cascade of damage and the mice behaved normally, said Erin Gibson, PhD, the study's leader and a former postdoctoral fellow in Monje's lab. It was the first time scientists showed that disruptions in interactions between multiple cell types in the environment around the neurons were the source of their aberrant behavior after chemotherapy, said Gibson, now an assistant professor of psychiatry and behavioral sciences.

In retrospect, the result seems logical, Monje said: "How can neurons function when there's all this dysfunction around them?"

After the paper describing this research was published in December 2018 in the journal *Cell*, Monje heard from cancer survivors from around the country who were relieved to find an explanation for the problems that had plagued them after treatment, she said.

"Many people wrote to me and said, 'Thank you. I didn't understand why I couldn't go back to work. Everyone thought I was just crazy or depressed. It's not that. This is real,'" she said.

"There needs to be increased awareness about cancer treatment-related cognitive impairment," she added. "People need to be counseled about this. They need to know there are scientists and physicians working to make this better, though we don't have the cure for it just yet."

'THIS WAS THE FIRST HOPE I'D EVER HAD SINCE MY CANCER. BECAUSE UNTIL THEN, ALL I'D HEARD WAS "IRREPARABLE DAMAGE." THIS WAS THE FIRST TIME I FELT THERE MIGHT BE SOMETHING THAT ISN'T JUST RELIEVING THE PAIN, BUT ACTUALLY MAKING THINGS BETTER.'

FINDING SOLUTIONS

When Liu read the article in *Cell*, she said, she practically cried with joy, knowing help might be on the way. "This was the first hope I'd ever had since my cancer," she said. "Because until then, all I'd heard was 'irreparable damage.' This was the first time I felt there might be something that isn't just relieving the pain, but actually making things better."

Monje said she'd like to test the impact on chemo brain of a compound that temporarily depletes microglia, such as Plexxikon 5622, as these cells are the trigger for the cascade of negative effects and require a reset to a more helpful, less harmful state. Her plan is to do more testing in animals with an eye to a clinical trial in a few years.

Meanwhile, scientists in her lab have pinpointed another possible treatment. Led by postdoctoral fellow Anna

Geraghty, PhD, they focused on a protein called brain-derived neurotrophic factor, or BDNF. Normally, neurons release BDNF, which does many things, including prodding oligodendrocytes to build myelin. But the researchers found that when the brain is exposed to methotrexate, the resulting microglial inflammation decreases BDNF made by neurons, and the oligodendrocytes lose their ability to form myelin in response to neuronal activity — a process, called myelin plasticity, that contributes to learning and memory. In the study, published in July 2019 in *Neuron*, the mice exposed to methotrexate had compromised brain function as a result.

In searching for a solution, Monje turned to Longo, forming a partnership that shows how scientific interests sometimes can converge in unexpected ways. Earlier work had indicated that BDNF latches on to the oligodendrocytes through a receptor called TrkB. It so happened that Longo had developed a small molecule, a kind of TrkB booster, that he was testing in the lab as a possible therapy for Alzheimer's, Parkinson's and Huntington's diseases.

The researchers tested the TrkB booster in the chemo-compromised mice and, remarkably, the animals' myelin normalized and their brain function was restored. Both Monje and Longo agree that the molecule, LM22A-4, could be a great prospect for treating chemo brain.

"This is a major step — when you discover an entirely new mechanism that is amenable to therapeutics," said Longo, the George E. and Lucy Becker Professor in Medicine.

Though Longo has had dramatic results using LM22A-4 to treat degenerative diseases in laboratory mice, he has not yet tested it in people. So it's not known how humans might respond to the compound, he said.

But there are many questions to be answered first, said Monje, such as when patients should receive drug treatment to counter chemo brain. In both studies, the treatment immediately followed methotrexate exposure. She's now studying the use of LM22A-4 at different points in time after cancer therapy.

"What if someone is still suffering from cognitive impairment 10 years later? Might this be a viable therapeutic strategy for them? Or is this something we have to do right after therapy?" Monje asked. "We don't know that yet."

Even the time of day treatment takes place could make a difference, said Gibson, who is a circadian biologist. She said studies have shown that the time of day patients receive chemotherapy drugs can dramatically influence the drugs' effectiveness. The same may be the case with drugs used to combat the effects of chemo and radiation.

"Are there times in the day when glial cells might be less susceptible to disruption by a chemotherapeutic agent? We have some early indications that may be true," said Gibson, who is pursuing this research in her lab at Stanford. "So there might be a therapeutic strategy in which just changing the temporal component of administration could mitigate some of these neurological deficits."

LOOKING FOR THE HOLY GRAIL

Monje said scientists also need to figure out why the changes in microglia after chemotherapy are so persistent. The cells remain activated long after exposure to methotrexate, meaning they are undergoing some fundamental change, she said. This persistence helps explain why patients continue to have cognitive problems years after treatment.

"Imagine you fell down and bruised your knee but your knee was inflamed forever," Fisher said. "Some of the drugs and radiation cause this permanent activation of inflammation. It's like you have a bruised knee forever. And that's a big problem."

Dietrich said the key to countering the damage is to create a nurturing environment for neurons.

"I think of that as the holy grail," he said. "Take the case of the tree that does not have enough water. It's not so much the tree that is the problem. It's the microenvironment that doesn't give enough to the leaves, and it falls apart."

Monje said it's not known whether other cancer drugs might have the same impact on the brain as methotrexate, which is a particularly bad actor when it comes to cognitive impairment. However, some research suggests a similar pattern among other cancer-fighting agents.

"There are other drugs for which direct activation of microglia has been described, but we should do a more comprehensive study of that," she said. "It may be different cancer drugs work through a different mechanism. Then we would need a different strategy."

Cancer survivor Liu said she functioned well for years after her treatment, completing her PhD at UC-Berkeley in English and becoming fluent in Mandarin and French. But one day in 2006, while teaching a class at Berkeley, she had a warning sign of things to come.

"I blanked out in front of the class I was teaching," she said. "I had to fake it and let the class out early."

She began to have increasingly frequent memory gaps.

"When it first started, it really frightened me," she said.

CONTINUES ON PAGE 38

WEB EXTRA: MICHELLE MONJE TALKS ABOUT CHEMO BRAIN. PODCAST AT STAN.MD/MONJEBRAIN

WALK WITH ME

FUTURE DOCTORS REALIZE THE POWER OF EMPATHY THROUGH EARLY PATIENT CONNECTIONS

By Mandy Erickson

PHOTOGRAPH BY TIMOTHY ARCHIBALD

MICHAEL FURZE AND TARA MURTY
Through a course that pairs medical students with patients, Furze and Murty bonded over musings about their lives, illness and finding hope in healing.

THEY SEEM AN unlikely pair, a young medical student and a retired programmer. But when Tara Murty and Michael Furze find each other on the plaza outside Stanford Hospital, they embrace. And when they tell the story of their friendship, they take turns speaking, deftly picking up where the other leaves off.

They met in September 2018 — "It was like a blind date," Furze said — as part of a class called Walk With Me for first-year medical and physician assistant students at Stanford University School of Medicine. The elective course pairs students with patients who have chronic and serious illnesses, or with their caregivers, for the nine months of the class.

At their first meeting, Murty and Furze sat on a bench outside the hospital. Over the course of an hour, Furze described his decadeslong struggle with skin cancer on his face and one of his shoulders, the surgeries that removed his nose and palate and then rebuilt them, drastically altering his appearance. Murty told of her upbringing in Amherst, Massachusetts, and her decision to attend medical school. And they soon discovered similarities: Both are originally from Massachusetts. Both love to read and write. And both like spending time outdoors.

They've since developed a strong bond, meeting once a month outside the hospital, even on chilly winter days. Together they began writing a book, a sort of co-memoir in which they discuss their histories, their friendship, their experiences, cancer and medicine. Each time they meet, they hand over the clothbound journal, taking turns to ink their thoughts onto its blank pages.

Murty describes moving to California, adjusting to the sun and the "entrepreneur energy" of her new home. Furze writes of his recovery from alcoholism, his winding career path and his cancer, which is in remission. They've kept writing and maintain the monthly meetings, even though the class concluded months ago.

After the trauma of illness and treatments, Furze has found the friendship to be therapeutic: "She has shown me that my experience is of value to people like Tara who are learning how to be a doctor and healer. It's simple talking with her. It has helped me sort things out."

For Murty, the class had an unexpected bonus: "I thought it'd just be a learning experience," she said. "But it's been such a joy to have a friend in Michael."

First- and second-year medical students typically spend little time with patients. They focus on learning the science behind medicine — anatomy, pathology, microbiology and pharmacology. They practice patient exams on actors, and they interview people in the hospital, but these encounters are brief; they don't get to know them personally, or learn their struggles with illness or the health care system. It's only during their third and fourth years that they start to encounter patients during their clinical rotations and under the supervision of physicians. Similarly, physician assistant students are involved in patient care only after completing five quarters of science classes.

But Erika Schillinger, MD, associate chief for education at the School of Medicine, said first- and second-year students had long been asking for contact with real patients beginning in their first weeks of medical school.

"These students very much yearned for an authentic connection with patients," said Schillinger, a professor of primary care and population health. She also wanted students to develop an understanding of the patients' views of medical care.

"We wanted to solidify empathy and compassion early," she said. "We want our students to have an appreciation for the whole of a patient's life, not just their illness."

Several years ago, Schillinger began planning for a way to foster empathy for patients early on, working with Kim Osborn, the school's director of education administration, and others. The result was Walk With Me: A Patient-Engaged Exploration of Health and the Health Care System. The course was first offered in the 2017-18 school year to 32 students, each one paired with a patient or caregiver. The school offers other classes in which students meet with patients, but only for a quarter; Walk With Me lasts an academic year. Such courses are part of a national trend in medical schools to give students a patient's perspective of living with an illness and navigating the health care system.

The pass-fail class meets once a month, and because it takes place in the evening, dinner is served. During the class, a faculty member and a patient speak about situations patients can encounter, such as trying to find their way around a website or having clinicians who fail to share information with one another. Students then brainstorm in small groups about

CONTINUES ON PAGE 38

A JOURNAL OF SHARED DISCOVERY

These are excerpts from a journal shared by Stanford University medical student Tara Murty and cancer patient Michael Furze, who were paired up in a Stanford program called Walk With Me.

CANCER PATIENT MICHAEL FURZE

"Cancer treatment has been long and hard, using up lots of my time. Doctors and hospitals have eaten up time and energy, leaving little time for building new memories to cherish."

"She was to receive the perspective of a patient. I was to get something else from her — a fresh young mind filled with hope and ambition. And empathy led to a great deal of healing. The perspective changed from damage to healing."

"As we share our lives with each other, we can both enjoy the lives we have while admiring and appreciating the life of the other."

MEDICAL STUDENT TARA MURTY

"Our conversations somehow comfortably move from the updates of medical school and the weather to talks of cancer, life and dying. The weight of these is so clear and yet it's easy to talk with Michael. He is so genuine and open — and I can tell he trusts me."

"Would he ever have imagined his life would be like this? Would he be surprised at the way he has shaped Stanford Medicine? How he has shaped me as I am becoming a doctor?"

"Sometimes randomness can bring together two people who maybe otherwise would not have intersected. From two different walks; different experiences; different ages, hometowns and favorite meals."

INSIDE A MOLECULAR TUMOR BOARD

USING GENOMICS TO GUIDE PERSONALIZED CANCER TREATMENT

By Krista Conger

ILLUSTRATION BY GÉRARD DUBOIS

"OK, PEOPLE, MUTE YOUR PHONES.

MUTE YOUR PHONES, PLEASE!"

The buzz in the first-floor conference room in the Blake Wilbur Building on the medical school campus slowly subsides as people take their places around a long table and in chairs set along one wall, plopping down and opening laptops to display medical charts and presentation slides. It's 2 p.m. on a Friday in December, and the Molecular Tumor Board is about to convene.

"Let's get started," says James Ford, MD, professor of medicine and director of Stanford's Clinical Cancer Genomics Program, loudly over the chatter of voices and jovial laughter.

Stanford's Molecular Tumor Board was launched in spring 2015 to use the molecular attributes of individual tumors and identify novel drugs that might help last-resort patients — those with advanced cancers that have resisted standard treatment. It's one of a handful of such efforts in the country. Since the board was created, the group has met twice a month to brainstorm about cancer cases referred to them from physicians inside and outside of Stanford. On the slate for the board on this day is a deep dive into two cases of women with cancer — one with breast cancer with an unusual combination of mutations and another with colorectal cancer.

Having an open mind is crucial. Traditional cancer care categorizes cases based on the type of tissue involved — is it in the lung, colon or breast, for example — and the stage at which the cancer was diagnosed. Has it invaded surrounding tissues or metastasized to distant sites? How large is the primary tumor? What are the patient's clinical symptoms?

Tumor boards across the country are usually similarly organized, bringing to-

gether experts from various medical disciplines to tackle cancers of particular types; Stanford has about 13 tumor boards focused on different tumor types, including breast, head and neck, thyroid and gynecologic cancers.

By contrast, Stanford's molecular tumor board is filled with experts who want to look under the hood of intractable tumors and identify, at a genetic level, what makes them tick. Together, oncologists, pathologists, cancer geneticists and genetic counselors, informatics experts, and medical fellows and residents comb through a labyrinth of data points, including any mutations in a tumor's DNA sequence that could be targeted by existing drugs. They also review patient treatment histories, which could determine whether the patient will qualify for a particular clinical trial or off-label treatment. Oncologists who wish to refer a patient to the board fill out a one-page referral form, and the patient's primary care team is encouraged to participate in the discussion in person or in a teleconference.

THIS SEA CHANGE IN APPROACHING CANCER TREATMENT IS, IN PART, A RESULT OF THE REALIZATION THAT CANCERS OFTEN SHARE mutations in key genes controlling cell growth or signaling pathways. It also is a result of new technological abilities that allow rapid DNA sequencing in a fraction of the time and cost. The National Human Genome Research Institute estimates that the cost to generate a high-quality human genome sequence was about $14 million in 2006; the same task, 10 years later, cost less than $1,500. Stanford's Solid Tumor Actionable Mutation Panel, which combines targeted sequencing with a bioinformatics analysis of known or suspected cancer-associated mutations, delivers results to patients' clinicians within three to four weeks — with insurance often covering the cost.

"We can now sequence hundreds and thousands of DNA sequences within a tumor in a time frame that is achievable," Ford noted. "And this group includes people very experienced in interpreting test results with lots of subtleties. Often we will identify tens or thousands of individual mutations in one patient's tumor. We need to decide: How do we prioritize these? Which are likely to be the driver mutations that the cancer relies on to grow? And, once we identify a potential targeted therapy, we discuss how to get that drug to the patient: Is there a clinical trial in which the patient could enroll? Might it be possible to get the drug for off-label use?"

Recommending therapies is one challenge; showing that they work and are cost-effective is yet another difficulty.

"We've definitely had instances in which people with widespread metastatic cancer have had tremendous responses to the targeted therapy we've recommended," said Ford. "The challenge is that, with this type of personalized medicine, we're not evaluating treatments in the standard way, with a clinical trial that enrolls many people. Instead, each patient is, in theory, unique — as determined by the combination of mutations found within their tumor."

Ford is leading a collaboration with Utah-based Intermountain Healthcare, which has the nation's largest repository of biological samples. By linking molecular data from the database of millions of samples to the health outcomes experienced by the people who provided them, researchers hope to advance the understanding of many diseases, including cancer.

"Intermountain can capture information about an entire population, so we can compare data about even very rare mutations and combinations and learn how best to treat these patients," Ford said.

But on this December day, Ford and his colleagues aren't thinking about the big picture. Instead they are hyper-focused on a few select cases referred to them by oncologists at Stanford Health Care and a few neighboring medical centers. In addition to two main patients, the team will, in rapid-fire fashion, consider seven others — some of whom had previously appeared before the board. Patient photos appear alongside their medical charts, and a familiar patient's case is greeted with a murmur of recognition and concern.

The team quickly gets down to business with a review of the relevant scientific articles from *Cancer Discovery* and *Nature*. Rochelle Reyes, a physician assistant who works closely with Ford on the tumor board, is the presenter. She details the molecular vagaries of an important signaling protein, analyzing how the patient's mutation is likely to affect the three-dimensional shape of the resulting protein and its ability to bind to other proteins to affect cell growth.

'WE CAN NOW SEQUENCE A TUMOR IN A TIME FRAME THAT IS VERY EXPERIENCED

"This particular mutant variant is very unique," Reyes notes, calling out a deletion that might drive tumor growth by causing the pathway to be abnormally active. "But if we try to block this pathway, this second variant protein might take over. Could PARP inhibitors be used in this context? It's unclear."

After about 10 minutes of review, the floor opens for discussion, mediated by Ford, who begins by handing out a printed page listing current information about clinical trials

at Stanford and elsewhere. "I think there are several potential options for this patient," he said, noting that he'd normally recommend a particular clinical trial, but "she's not eligible because of these other mutations."

More suggestions fly, fast and furiously around the table as the team considers other clinical trials. "We have a trial opening in the next few months testing an inhibitor that might work, but colon cancers are not eligible," Ford sighs. "That's too bad, because that sounds kind of perfect."

Eventually, the team decides to refer the patient to the MATCH trial, or Molecular Analysis for Therapy Choice, run by the National Cancer Institute. Similar to Stanford's tumor board, the MATCH trial — of which Ford is a co-director — seeks to assign patients, many with uncommon cancers or combinations of mutations, to targeted treatment arms based on a molecular analysis of their tumors.

"Some of these genetic changes are extraordinarily rare," Ford said, "so some of these trials recruit participants from around the country. The first version of MATCH had 36 different arms, each focused on one specific mutation, regardless of tumor type, which was matched to treatment with a particular drug. Now we're launching a new version of MATCH in which we'll test the effect of drug combinations against specific mutation combinations. This is the next iteration in genomic medicine. Each tumor has so many genetic changes that it's likely we are going to need to tackle multiple targets to be successful."

The next case, presented by Paolo Ocampo, MD, PhD, a clinical fellow in molecular genetic pathology, highlights details from a patient whose tumor has evaded all standard treatments. Unfortunately, the mutations found in the tumor defy the standard methods of subcategorization that often aid treatment decisions for breast cancer. There appear to be two main drivers of tumor growth, but the patient also has a third mutation that often results in resistance to treatments targeting those drivers.

"Most importantly, is she eligible for PUMA?" muses Ford, referring to a trial testing the effectiveness of a drug called neratinib in tumors with similar mutations as the patient's. "We have a trial that includes these mutations — that would be a great trial for her."

"She's just started treatment locally, but she's coming to see us soon," says Reyes.

Quickly, the board addresses several other cases: breast cancer with brain metastases that must be stabilized for the patient to qualify for enrollment in a clinical trial, a head and neck squamous cell cancer with an interesting gene rearrangement, pancreatic cancer with a mutation that excludes the patient from many clinical trials, and a rectal cancer with a rare mutation. "We need something for ATM mutations," says Ford in frustration. "I don't know what to give this guy."

FINALLY, THEY CONSIDER THE CASE OF A YOUNG PATIENT WHOM MANY IN THE ROOM RECOGNIZE. THEY'VE DISCUSSED HER BEFORE, BUT HER CANCER is growing again. "My guess is that her cancer is progressing because only a portion of her cells are susceptible," says Ford, of the previous treatment. The team brainstorms new approaches before breaking up for the afternoon.

"The board serves as a way for us all to share what we're learning about new studies and new drugs," Reyes said. "Sometimes the answer for a particular patient is obvious, or maybe someone in the room has a tidbit of information the rest of us don't have."

A note documenting the board's discussion is included in each patient's chart for the referring oncologist.

"Our hope is that this type of approach will be successful not just for metastatic patients who don't have options, but that what we learn here might also help to bring this personalized oncology to newly diagnosed patients to increase cure rates and decrease the toxicities that often accompany traditional therapies," Ford said.

HUNDREDS AND THOUSANDS OF DNA SEQUENCES WITHIN ACHIEVABLE. AND THIS GROUP INCLUDES PEOPLE IN INTERPRETING TEST RESULTS WITH LOTS OF SUBTLETIES.'

"While the immediate objective of the Molecular Tumor Board is to assimilate evidence that informs treatment decisions for individual patients with advanced disease, the data generated through this process also allows us to advance precision medicine more broadly," said Christina Curtis, PhD, associate professor of medicine and of genetics at Stanford and co-director of the board. "In particular, it provides an important source of real-world evidence as to the relationship between the molecular profile of a patient's tumor and their response to a given treatment. While each patient is unique, as is their cancer genome, we can learn important

CONTINUES ON PAGE 39

'I LOVE PAUL FOREVER'

The late Paul Kalanithi's memoir, *When Breath Becomes Air*, has been heralded as an unforgettable piece of literature. Shortly after learning he had stage 4 lung cancer and the reality of the prognosis set in, the Stanford neurosurgeon began writing about his walk toward death. The book is written with humor, grace and searing honesty.

SHEPHERDED TO POSTHUMOUS publication by his physician wife, Stanford internist Lucy Kalanithi, and released in 2016, the memoir has been stamped as monumental and stirring. One critic wrote, "It's a story so remarkable, so stunning and so affecting that I had to take dozens of breaks just to compose myself enough to get through it." It spent 68 weeks on the *New York Times* bestseller list and has been translated into 39 languages.

It's been five years since Paul Kalanithi's death. Lucy Kalanithi and daughter Cady, now 5, have moved to a new home. Kalanithi fell in love again. But they still visit Paul's grave, nestled at the edge of a field in the Santa Cruz Mountains. The setting is majestic, with a view of the Pacific Ocean just a few miles away. They picnic, bring flowers and, as Kalanithi wrote in the epilogue to *When Breath Becomes Air*, she rubs the grass "as if it were Paul's hair."

"Paul's decision to look death in the eye was a testament to not just who he was in the final hours of his life but who he had always been," she wrote in the epilogue. "For much of his life, Paul wondered about death — and whether he could face it with integrity. In the end, the answer was yes. I was his wife and a witness."

Kalanithi continues to speak publicly about their family's legacy, including a recent conversation with contributing editor Paul Costello at the San Mateo Public Library. They spoke about some of her memories of life after her husband's diagnosis and what it means to move on after the death of a loved one. This Q&A is based on that conversation.

COSTELLO: Now, a few years after Paul's death, what's it like to read his words from the book at public events?

KALANITHI: It's really nice to read it for a lot of reasons. I love hearing Paul's words. … It makes me feel connected to him; I'm participating in part of what we have been doing together. I'm proud of him.

COSTELLO: Recently, Britain's Prince Harry was talking about the death of his mother, Princess Diana, and he said grief is "a wound that festers." Does that ring true to you?

KALANITHI: Did he really say that? That's so sweet and sad. … I don't think of it as a metaphor like that, partly because as a doctor I'm like, "Well, if a wound festers, it's really untended." I agree with the part of it that's implying it's not just going to close up and then be this neat little scar. There's a wound. But my experience of grief has changed over time.

COSTELLO: How so?

KALANITHI: In that first year, there was a sadness and loneliness and anxiety that I didn't expect. Doing a book tour for Paul was extremely helpful because people asked me about him a lot. Instead of treating me with kid gloves, people would just walk up and say, "I read your husband's book. Here's what I think." It was this real entree into feeling less alone. Now, I feel like that pain has lifted a lot, but I love Paul exactly the same amount. So to me, the love feels very salient.

'In that first year, there was a sadness and loneliness and anxiety that I didn't expect. Doing a book tour for Paul was extremely helpful because people asked me about him a lot. … It was this real entree into feeling less alone.'

COSTELLO: When you discovered Paul was seriously ill, you must have had two reactions. One as a wife and another as a physician.

KALANITHI: He logged into a hospital computer. It was very clear on the CT scan. Suddenly, all these symptoms were explained. It was like standing between the past and the future. It was very, very clear that we were looking at an incurable disease. It was really disorienting. Then there was the challenge of facing your mortality. Paul wrote, "The

future I imagined evaporated." I think we talked in bullet points. Paul said, "I don't want to die." We would whisper things to each other at night for a while.

COSTELLO: In all of that intensity, how did you decide to have a child?

KALANITHI: It seemed pretty crazy to do that. Paul was more sure than I was that he wanted to have a child. I said, "It's going to make it really hard. You're really sick. I worry that having to face dying and having a new baby who you need to say goodbye to is going to make it really hard. What do you think about that?" He said, "Wouldn't it be great if it did make it really hard?" It was such a lovely statement of what our lives are about. Sometimes you cannot have joy without risking pain.

COSTELLO: How did you handle having an infant on one hand and a dying husband on the other — both with significant needs?

KALANITHI: I found, when Paul was sick and in some ways with being a mother, this ferocity of love. In a way, I felt invincible because of love, like, "Whatever happens, it'll be OK." I used to think of life as a path — it's going somewhere and you walk on it. Or life is a mountain and you're going to climb it to the top. Now I think life is a series of moments. When Paul was sick, I could see it as a moment. Same with Cady being a baby. I was like, "This person needs me and this person needs me, and that's what I'm doing right now."

COSTELLO: You've said Paul didn't die until he died. What do you mean by that?

TIMOTHY ARCHIBALD

Lucy Kalanithi often visits the gravesite of her husband, Paul Kalanithi, with the couple's daughter, Cady, to picnic and leave flowers.

KALANITHI: I was talking about watching Paul wrestle with his mortality and try to figure out how to shape an identity. There was just so much messy intellectual and existential work that he was doing even as his body was declining, betraying him and collapsing. There was a striking contrast for me. His body was dying, but his sense of self, intellect or engagement wasn't. Being able to be a writer after needing to stop being a surgeon was a huge part of that. I think it's Nietzsche who said, "He who has a why to live

CONTINUES ON PAGE 39

The right moves

TRACKING SURGEONS' MOTIONS TO UNDERSTAND SUCCESS

By Hanae Armitage

CARLA PUGH DEVELOPS SENSORS — INCLUDING THESE — THAT TRACK SURGEONS' HAND MOTIONS.

DEEP IN THE HALLS OF SAN FRANCISCO'S Moscone convention center, surgeons gathered near the far corner of a conference's exhibition space, attracted by a somewhat unusual scene: 10 identical tables, each topped by a tray of surgical tools, several bundles of sutures, a stopwatch and a section of pig intestine. An ice chest sat on the floor, its contents labeled in large lettering: OLD BOWEL.

Just outside the waist-high barriers of the display, Carla Pugh, MD, PhD, a Stanford professor of surgery, mingled with curious passersby. "Would you like to know more about our study?" she asked. Pugh was at the world's largest surgical conference, the American College of Surgeons Clinical Congress, which was held in late October, and she was taking advantage of the foot traffic.

"We're recruiting surgeons for our

research, which uses several types of sensors to measure a surgeon's movement during an operation, their decision-making and their brain waves," she told a group of interested participants.

The more adventurous of them stepped forward and were presented with a scenario: A "patient" — a chunk of pig bowel — was in need of a small surgery. Each piece of tissue had been lacerated in two places. The participants were charged with finding the damage and repairing it — all under the monitoring of several data-collecting sensors, while being timed.

The surgeons palpated and gently pulled at the edges of the pink, crinkled bowel to locate the tears. With their choice of suture and stitching technique, they mended the intestine to their satisfaction. When they were finished, they called for their time and stepped back to let the study's assistants evaluate the work.

The goal of the exercise was to collect metrics on a basic surgical procedure — repairing a tear with sutures — and use the data to understand how specific motions, decisions and approaches correlated with the quality of the work. The event was one of the first showcases of a vision that Pugh has developed for decades: applying data, for the first time, to understand what it is that surgeons do and how they do it.

"In the field of surgery, there are no metrics to back up what it is that we do, or the range of tactics we employ to get positive surgical outcomes," said Pugh, who is the director of Stanford Medicine's Technology Enabled Clinical Improvement Center. "We walk around with more detailed data about our bank accounts than how we perform clinical procedures, which are 10 times more complex. But I'm hoping to change that."

GEARING UP FOR DATA COLLECTION

PUGH'S RESEARCH, part of a new multi-institutional collaboration called the Surgical Metrics Project, which she leads, harvests data from audio and video recordings of surgeons and wearable sensors that measure motion, brain waves and tactile pressure. She's one of the first researchers to study surgical data analytics, a subspecialty that she guesses comprises only a few dozen experts.

'We walk around with more detailed data about our bank accounts than how we perform clinical procedures, which are 10 times more complex.'

When Pugh began pursuing this line of research, surgical wearables did not exist; in fact, the rise of everyday wearables like the smartwatch was still 10 years away. Her interest in the subject stemmed from an insight that struck her as a young scientist. "In medical school, I saw that technology had huge potential to facilitate medical education and training," Pugh said. "And so I took a bit of a detour through my own training and ended up getting a PhD in education and technology from Stanford's Graduate School of Education."

SURGEON ALBERTO FELIPE TORRES OF SANTIAGO, CHILE, REPAIRS A TORN PIG BOWEL FOR A STUDY ANALYZING THE MOVEMENTS, BRAIN WAVES AND DECISIONS OF SURGEONS DURING OPERATIONS.

One of her graduate classes focused on human-computer interactions and sensor technologies. She began to understand how technology could enhance clinical performance and became convinced that data-collecting sensors were the key to teaching hands-on skills in a way that a textbook, video or lecture never could. Some of Pugh's earlier work in wearables grew out of her experiences in cancer detection — for instance, a bra that collects data during a breast examination through force sensors built into the fabric.

Fast-forward to today: Pugh's suite of operation-friendly wearables is gaining attention in the surgical community. In the past few months alone, Pugh and her team have collected data from hundreds of surgeons — the bulk of which came from conference-goers eager to donate their time and test their skills.

Andrew Wright, MD, a surgeon at the University of Washington, was one of the attendees keen to try Pugh's technology. "I'm highly involved in surgical education and training, and I've known Dr. Pugh for a number of years through our shared interests," Wright said. "This sort of technology could be used not just for training students and residents but also for helping practicing physicians maintain their skills and learn new surgical techniques."

There are two key elements to successful integration of the technology, said Pugh: One is sleek, user-friendly wearables; the other is integrated data streams. The trick is to collect as much information as possible without impeding the natural pattern of a surgeon's workflow.

CONTINUES ON PAGE 40

OPPOSITE: EDWARD CALDWELL; RIGHT: RACHEL BAKER

'Making science fiction come true'

AN EXCERPT FROM *DISCOVERING PRECISION HEALTH*

A world without disease seems impossible, but is it? A new book by Lloyd Minor, MD, dean of Stanford University School of Medicine, makes the case that this futuristic vision is within our grasp. In *Discovering Precision Health: Predict, Prevent, and Cure to Advance Health and Well-Being*, Minor explains: "We are in the midst of a revolution in science and technology related to the mechanisms of disease and, of equal importance, to the determinants of health and well-being. The impact of these advances and their broad dissemination are going to have a profound effect on our ability not just to treat diseases but to prevent them from developing in the first place. And in those instances when diseases cannot be prevented, they will be diagnosed much earlier and therefore treated much more effectively."

The book lays out the barriers to achieving this vision, proposes solutions and gives examples of progress already being made. Among those examples are many originating at Stanford, including this one offering hope for a permanent fix for an agonizing skin disease.

The book, co-written by Matthew Rees, was published in March by John Wiley & Sons Inc. Proceeds will go to Stanford University.

EXCERPT

TREATING A PAINFUL AND DEBILITATING SKIN CONDITION

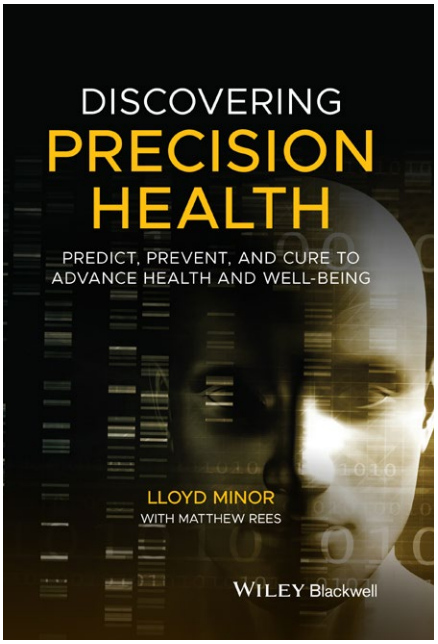
A rare skin disease called epidermolysis bullosa (EB) is among the most painful and debilitating conditions ever diagnosed. "The word 'pain' itself doesn't even describe how bad EB is," said one courageous young man, Paul Martinez, living with the condition, in a 2015 film about EB patients called *The Butterfly Effect*. "Your body is constantly on fire — it burns from the wounds from raw flesh, and it keeps repeating over and over and over. The cycle is never ending."

Approximately 1 in 200,000 babies is born with EB. There are different subtypes of the condition, but a common one is caused by the absence of a gene that results in the skin being unable to make something called anchoring fibrils. They are primarily composed of collagen and function like a staple — keeping the top layer of the skin (the epidermis) attached to the next layer (the dermis). As a result, for people with EB, virtually any force applied to the skin leads to blistering and that part of the epidermis falling away. These wounds never heal, resulting in mutations that trigger metastatic skin cancer and take the lives of many of these patients.

In the absence of any treatments for EB, most of those with the disease have not lived past their mid-20s. But in recent years, Stanford dermatology professors have been making steady progress in developing a treatment that can deliver life-changing wound healing treatments for EB patients and potentially help remedy other, more common conditions.

One of those Stanford professors is Jean Tang. She and some colleagues in the dermatology department have been working on a therapy called EB101, whereby they take somatic keratinocyte cells off a patient's skin, use a retrovirus to reinsert the gene, and then graft those cells onto the patient. A Phase 1 clinical trial showed that these grafts are safe and lead to durable wound healing for up to four years and counting. A Phase 3 clinical trial was set to begin in mid-2019, and positive results would mark an important step toward one of the ultimate goals: securing FDA approval for a drug to treat EB.

Anthony Oro, the Eugene and



Gloria Bauer Professor of Dermatology, is working on the next generation of therapy to treat EB. His focus is developing a product that would cover the wounds of EB patients and permanently heal those wounds — and do so at an early age so that they don't get skin cancer from the chronic wounding.

His research aims to develop a scalable manufacturing platform to make

large amounts of corrected tissue stem cells. In 2014, Oro was one of the authors of a study with Marius Wernig, an associate professor of pathology at Stanford. The study showed that it was possible to create induced pluripotent cells from the skin cells of EB patients and then replace the disease-causing gene with a healthy version of the gene. ("Making science fiction come true," says Tang.) Oro described this development as enabling "an entirely new paradigm for this disease."

"Normally, treatment has been confined to surgical approaches to repair damaged skin, or medical approaches to prevent and repair damage. But by replacing the faulty gene with a correct version in stem cells, and then converting those corrected stem cells to keratinocytes, we have the possibility of achieving a permanent fix — replacing damaged areas with healthy, perfectly matched skin grafts."

This process involves the use of autologous CRISPR-corrected induced pluripotent stem (iPS) cells. These cells are made by collecting cell samples from someplace easy to access, such as skin or blood. The cells are then treated in a dish with a combination of genes that enable them to go back in time — a process known as cell reprogramming — so that they resemble the cells from which all tissues are formed. John Gurdon and Shinya Yamanaka were awarded the Nobel Prize in Physiology or Medicine in 2012 for this pioneering work in regenerative medicine.

"The CRISPR technology was very efficient," says Oro, "and it allowed us to develop a very robust, one clonal step manufacturing protocol to make the autologous CRISPR corrected iPS cells." (Previously these cells were being derived through multiple clonal steps, which brought more risks, as they were in culture longer and subject to more mutations.) The effect was to reduce cost and increase safety and to mark a shift from "this could be done" to "now it's being done less expensively and with more safety."

'Even if I can't get any benefit from it … I just want the disease to stop for the future. … I've been blessed to live longer than most people with this disease.'

This process has also made it possible to grow the cells in much larger quantities. The next step is inducing activity of the cells to make the skin, which results in a thin sheet of skin cells derived from the iPS cells. Like EB101, these sheets are akin to a Band Aid that's roughly the size of a smartphone. Each one is laid onto a patient's wound, and it then grafts onto the patient's skin. The benefits are realized almost immediately, says Oro, as the grafting heals the wounds. "Kids can walk around and not have to worry about what will happen if they accidentally bump into something."

Today, the grafts are small and only cover a small fraction of a patient's skin. The ultimate goal is to have the graft cover all of a patient's skin — and perhaps even for the product to come in a liquid form that can be sprayed onto the patient's skin.

As with so many other medical and technological discoveries developed for the treatment of a rare disease, the same technology can then be generalized to more common diseases. The iPS technology has a range of potential applications beyond EB. Oro points out that the therapy can be very effective for wounds that are slow to heal or don't heal at all — such as those caused by injury, burns, or diabetes. The technology of making tissue from iPS cells that have undergone genetic manipulation is also being used to make stem cells for other tissues. There is already research underway on the thymus, the bladder, and even the heart. Tang points out that much of the progress that's been achieved is the result of many years of basic research (particularly in the area of recombinant DNA) as well as powerful tools (like electron microscopy) and tests that reveal valuable information (like indirect immunofluorescence). "It's very gratifying when all of these elements come together to give a patient hope that their suffering can be reduced — if not eliminated."

The many potential applications for the skin grafts are encouraging, and we remain hopeful that there will be continued progress in developing a remedy for EB that can end the suffering of those with the disease. Paul Martinez, whom I mentioned at the start of this section, has participated in EB clinical trials, and he's said that the results have been promising.

"Even if I can't get any benefit from it … I just want the disease to stop for the future. … I've been blessed to live longer than most people with this disease. But it's kind of bittersweet. Thirty-five years is a long time to live with the pain that I go through. And I don't want any children to go through that. If I'm in a position where I can help the future of EB, then I'm going to do it." **SM**

FEATURE

Mind jumble

CONTINUED FROM PAGE 25

"I thought, 'Am I losing my mind?' The only thing I can do is rest my brain. I just lie down and focus on breathing, without distraction. It helps."

She runs most days but lacks the stamina to do any more marathons. She's been studying biochemistry online in very short spurts — she wants to be able to understand the science behind her condition. And she's writing a book about her experiences, cobbling together previous publications and years of notes, but she has limited mental energy for writing now.

Monje says Liu has done extremely well over time, particularly considering that she was exposed to intensive chemotherapy and cranial radiation.

"She is remarkable in how much she has accomplished despite these major challenges," Monje said. "It is so frustrating for me to see my patients like Sarah struggle with these daily burdens and not be able to offer more restorative therapy yet."

Liu said she feels immense value in the doctor-patient relationship, as she and Monje "have a shared understanding of the cost of chemo, grief as we watch the decline, knowing that we are doing the best we can at both ends, for ourselves and untold others." SM

— Contact Ruthann Richter at medmag@stanford.edu

FEATURE

Walk With Me

CONTINUED FROM PAGE 27

the situations, seeking better ways to offer care. They meet with their patients at least once a month; once a quarter, the patients join the students in class.

Olivia Jee, MD, one of the course's instructors, said that in traditional physician training, "you learn medicine from a clinician's standpoint. You can get jaded and see patients as diseases. I like the idea of reminding students along the way of why they went into medical school."

Lloyd Minor, MD, dean of the School of Medicine, added that the class helps train medical and physician assistant students to provide empathic, personalized care. "One of the best tools a caregiver has is the ability to listen," he said. "By understanding what patients go through, what their concerns are beyond the appointments and treatments, the students learn to care for patients as individuals who have their own goals and hopes for the future."

The course requirements are kept to a minimum, given the demands on first-year MD and PA candidates. Students are assigned optional reading before each class, and they write a short reflection afterward. At the end of the year, the students are asked to produce, with their patient partners, something that reflects what they learned from their relationship. Murty and Furze turned in their co-memoir, while other pairs have developed a recipe, composed a song, designed an app or created artwork.

The students arrive the first day of class "fresh and nervous," said Jee, assistant professor of primary care and population health. "Sometimes they're worried about how to talk with their patient partners, but over the year they develop genuine relationships."

Not every pair develops the kind of lasting friendship Murty and Furze have, but they generally find a way to connect. One pair — assigned randomly, as all the pairs are — discovered they had attended the same junior high school in Hong Kong.

Many of the patients are volunteers from one of the hospital's patient and family advisory councils, some are Stanford Health Care employees, and others are referred by Stanford nurses and doctors. They are transplant recipients, cancer survivors and sufferers of various chronic illnesses, or they are caregivers of patients who are so ill they are unable to participate in the course. Students are expected to accompany their patients to one medical visit during the year.

Jee said she wants the students to leave the course understanding not only how to be more caring clinicians but also how to improve the practice of medicine overall. "I hope they learn that they can have a lasting impact on patients' lives, and that they can change medicine into something that really is patient centered," she said.

Furze signed up to be a patient partner for Walk With Me because, he said, "I wanted to help shape the minds of future doctors. I wanted to share with a medical student how difficult it is to navigate the medical process."

As a teenager in Arizona in the late 1960s and early 1970s, Furze worked as a lifeguard and was exposed for hours to the blazing sun. "Nobody was really worried about sunscreen back then," he said.

In 1983, Furze's physicians found a large basal cell skin cancer on one of his shoulders and removed it. For years afterward, he regularly had small precancerous lesions removed. Then, in 2012, skin cancer developed on his face. He has undergone six surgeries as well as radiation treatment.

The therapist who helped him recover from the trauma of the illness and surgeries thought that if he sat on Stanford's Patient and Family Advisory Council, it would help him view his experience as something that can benefit others. He took her advice, joined the council and

volunteered for Walk With Me.

Getting to know Murty, he said, "humanized the health care professionals for me. I have realized what a major undertaking becoming a doctor is. It made it possible for me to see doctors as people who are able to make mistakes as well as treat disease."

Murty, an MD-PhD student, registered for Walk With Me because she thought it was "a really special opportunity to get to know a patient personally."

Once she becomes a physician-scientist, she hopes to conduct medical research that's informed by problems she encounters in practice. Next year, she plans to pursue the PhD side of her degree, working in the lab of Crystal Mackall, MD, the Ernest and Amelia Gallo Family Professor. Mackall, who specializes in pediatric cancer, is conducting studies of CAR-T cell therapy, in which patients' own immune cells are genetically modified to fight cancer.

Murty said that telling Furze about her laboratory work confirms her desire to conduct cancer research. He's curious about her projects, which spurs her to seek new discoveries: "The projects may not yield results that change patients' lives immediately but can certainly give them hope," she said.

She added that Furze has shown her "how cancer impacts lives in so many ways."

"Michael's friendship has reinforced in me the kind of doctor I hope to be — one who cares deeply about the physical, mental and emotional health of my patients; one who understands my patients' lives, joys, vulnerabilities and fears; and one who is a partner to my patients."

She added, "There's so much value in knowing the experiences of patients. I've learned that some of the best care doesn't have anything to do with knowledge. It's just about listening and respecting a patient's concerns." SM

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FEATURE

Inside a molecular tumor board

CONTINUED FROM PAGE 31

patterns from that data by aggregating this information across many patients. Ultimately, this — in conjunction with other data — may lead to new, more effective, therapeutic strategies."

In 2017, Ford and Lincoln Nadauld, MD, PhD, executive director of Intermountain Precision Genomics, studied 72 patients with metastatic cancer: Half had undergone genomic testing followed by targeted treatments based on their cancers' mutations, and the other half were treated with standard therapies. The study showed that the group who received targeted treatments experienced a longer period before their disease progressed and did not have greater health care costs than the control group.

Ford lingers after the meeting to talk with a colleague. "I really hope we get feedback on these cases," he says. Feedback is critical to the tumor board's mission to stay ahead of every patient's cancer, every time.

"We're always planning out the long game," Reyes later said. "We want to know not just what to put the patient on now but what we're going to put them on next, and then what we could put them on after that. So the instant a patient needs to start a new treatment we have already planned that transition. The whole point of the tumor board is to get the most promising treatment to patients as quickly as possible." SM

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FEATURE

'I love Paul forever'

CONTINUED FROM PAGE 33

can bear almost any how." He felt this immense sense of reshaped purpose and was able to tolerate a fair amount of suffering, physically, because of pursuing his purpose.

COSTELLO: You wrote a column for the *New York Times* entitled, "My marriage didn't end when I became a widow." What did you want to say?

KALANITHI: I love Paul forever. He's my family forever. I read C.S. Lewis' *A Grief Observed*, where he wrote, "Bereavement is not the truncation of married love but one of its regular phases." I thought it was beautiful. There is someone left in a marriage, even after someone dies, like that is a phase of your marriage. I really related to it.

COSTELLO: What do you want your daughter to know about her dad?

KALANITHI: Paul didn't leave her a letter or any other message directly to her, apart from the book. To me, within the book, he talks about what he thinks is meaningful. He talks about the importance of striving. He talks about the challenge of facing mortality. Then he says "I love you" at the end. I think that's a pretty decent message to impart as a parent. It's like, "I want you to be a good person. I want you to try hard, and I love you." … It's very nice to have this solid thing that she can find.

COSTELLO: In the final days of Paul's life, what was most important to him? What was most important to you?

KALANITHI: People dying often have one North Star. For Paul, it was to be mentally lucid. That helped us with the decision-making, too, in the hospital. He had to make this decision of whether to be intubated on a ventilator machine,

a breathing machine. Both being doctors, we knew for a patient like him, it likely wouldn't help and he'd probably stay sedated or stay in a coma, not really able to breathe on his own or go home or wake up. Then he decided not to do it, which was really brave and hard. Even as a doctor, it was really, really hard. His desire to be lucid was so clear to him, so clear to me, it helped make that decision.

COSTELLO: What did you learn about yourself in the final moments preparing for death?

KALANITHI: For Paul, the upending moment was diagnosis. For me, the upending moment was Paul dying, which may be sort of obvious. I think I was so surprised, for lack of a better word. Even though I wasn't surprised by the fact of it, it was very hard to walk out of the hospital. I could barely move my legs walking out of the hospital. I think the idea of holding two things, holding joy and holding pain at the same time has been prominent for the past few years for me.

COSTELLO: After you lose a loved one, at some point you'll have to go through a closet and take out clothes. You'll have to go through objects and put them away. How did you decide when that was appropriate?

KALANITHI: I just sort of realized when I woke up one day that maybe today's the day. For six months, Paul had his shoes on the floor, a bookshelf with his books on it, a toothbrush. It felt like there really wasn't a hurry. I was like, "These are still here. Right now, that feels really good. Maybe someday it won't, so if they start feeling like they shouldn't be there, then I'll put them somewhere." Six months later, I started to do that. About a year after Paul died, my sister remodeled my whole apartment. I never would have wanted to do it sooner. Then once it was done, I was like, "This feels so fresh, and I suddenly feel fresh." It's the kind of thing where you just have to trust your instinct.

WEB EXTRA

Hear the conversation at stan.md/KALANITHITALK

This interview was condensed and edited by Paul Costello

PLUS

The right moves

CONTINUED FROM PAGE 35

As part of the study, each surgeon first undergoes a baseline electroencephalogram, which measures brain waves through wires encased in a brown, translucent sensor strip that sticks to the surgeon's forehead. The strip measures brain activity while the participant performs a handful of mundane mental tasks: about 10 minutes of listening to music, meditating and recalling certain melodies.

Then, the surgeons suit up for data collection, each donning a special lab coat that holds a variety of wired sensors. Three motion sensors — so fine they fit under surgical gloves — poke out of the sleeves and are secured to the thumbs, index fingers and wrists with a piece of tape.

Finally, Pugh sets up audio and video recordings, which run as surgeons operate. The integrated approach to data collection shows not only how the surgeons' hands move, but also how they talk through tricky parts of a procedure, and how their brain waves spike or dip.

THE PROOF IS IN THE DATA PATTERN

SO FAR, THE IDEA of surgical wearables has been met with mixed reactions, Pugh said. Mostly, there's a sense of excitement and an eagerness to participate, she said. But there's concern, too — namely, that the data would be used to unfairly judge a surgeon's skills during a difficult procedure. It's true that the wearables could be used to one day test surgical skill or review a case that went awry, but to Pugh, it would be a mistake to limit the data to that purpose.

"To me, collecting surgical data is less about evaluating the skill of a surgeon and far more about quantifying what it took to take care of a specific patient," Pugh said.

She gives an example: Patients in intensive care units often need a central line, a type of IV that can withdraw fluid or deliver medicine. But inserting a central line into the vein of a frail 90-year-old patient is extremely different from doing so in a morbidly obese patient, or in a patient who has had multiple lines placed in the past, which can cause scar tissue and change how a vein is accessed.

"We all know the difference as practiced physicians, but there's no data to show it," Pugh said.

Pugh and her team are still just getting off the starting blocks, but the data they've collected — through recent, resident-fueled pilot studies and at a handful of medical and surgical conferences — have already started to yield intriguing insights through data patterns.

Instead of analyzing every data point from a surgery, researchers look for trends. The motion-tracking sensors feed visual data back to a computer, revealing movement patterns of a surgeon's hands, including where they pause and where they spend more time.

"People would ask me, 'Why would you want to measure surgical technique? Everyone operates so differently.' But our data essentially shows the opposite," Pugh said. "Whether surgeons use different instruments or add their own finesses to a procedure doesn't really matter."

The overall movement patterns that are generated are very similar, so long as there aren't complications — such as abnormal patient anatomy or the rare surgical error.

Such data patterns can show where surgeries hit a snag. Take, for instance, some surgery with a movement pattern that looks roughly like the body and wings of a butterfly when performed successfully. Those who perform that surgery without complications will see that same butterfly-esque movement pattern. Those who don't might have a pattern with lopsided wings or one with two bodies. "The motion sensors that track that surgeon's fingers and hands produce a very visual result," Pugh said. "And what's even more interesting to see is that there doesn't seem to be a correlation with instrument choice or whether the surgeon switched step 5 for step 6 — it's the patient's anatomy that most accurately correlates to the end pattern."

BIG (DATA) DREAMS

THE INTERTWINING data streams from various wearables on the surgeon's body can reveal quite a bit about the procedure and the patient on the table. But more than that, Pugh and her colleagues also see it as a data-first approach to teaching, learning and improvement.

"The innovative research led by Dr. Pugh's team will provide incredible data-informed insights into surgeon efficiency of motion, tactile pressure and cognitive load while performing a variety of medical and surgical tasks," said Mary Hawn, MD, who chairs the department of surgery and is the Emile Holman Professor of Surgery. "These types of data could be used to identify when a surgeon has mastered a procedure and when there may be a deficit."

WEB EXTRA

Measuring the metrics of surgery. Video at stan.md/2UP72M9

Some of the wearable applications are still a ways off from use in the operating room, Pugh said, as the technology is now used only for procedures on manikins and tissue bits. But there is one wearable Pugh has tested in patient surgeries: the electroencephalogram, or EEG, sensor.

During two surgeries, a gall bladder removal and an appendectomy, Pugh has volunteered to stick the brain-wave-reading sensor onto her forehead. "First, we just need to verify that it works in the OR and that the data comes in successfully," Pugh said. So far, it does. Through the EEG data, Pugh's team could see that the peaks of Pugh's brain waves while operating corresponded with the most trying moments of the surgery, while lower level activity synchronized with menial surgical tasks, like suturing.

After a successful surgery, Pugh closed the patient and left the operating room, forgetting to remove the long strip on her forehead. "My colleagues who are aware of my research saw the EEG sensor and immediately knew what I had been doing," she said. Now, Pugh's often peppered with the same question: When can others test out the technology?

"This is an entirely new data endeavor; we're learning in real time how best to propel this work, analyze the data and fast-track it in a safe way so that other surgeons can begin to use it in their ORs, too," Pugh said.

"Right now, it's just me who's tested it during surgery, but my big dream is to have this be routine. I can't tell you all the ways the data will be used, but it will definitely improve the care we provide." **SM**

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UNSCRAMBLED EGGS

A SCIENTIST'S EYE FOR DETAIL CATCHES MIXED-UP FROG CELLS REASSEMBLING

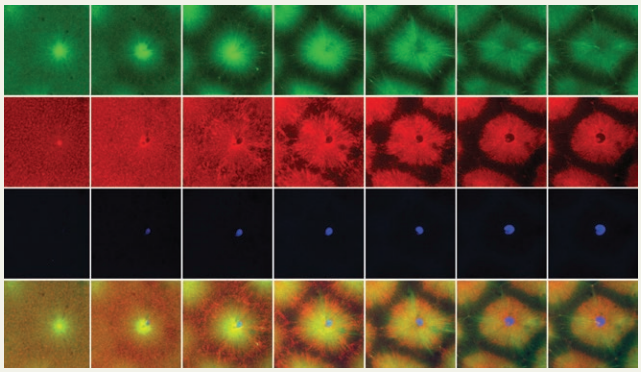
Smashing up frog eggs isn't as permanent as it seems — the resulting goop can unscramble and form distinct cell-like compartments. "We were gobsmacked," James Ferrell, MD, PhD, said of the discovery. "If you blend a computer, you'd end up with tiny bits of computer, and they wouldn't even be able to add two and two. But, lo and behold, the cytoplasm reorganizes," said Ferrell, a professor of chemical and systems biology and of biochemistry.

Previous studies have shown that some of the tiny living machines inside cells can self-assemble from their purified components, but the new study provides the first example of self-organization at the scale and complexity of entire cells. And though these compartments fall short of real frog eggs — they can't go on to form tadpoles — the discovery is eye-opening for scientists interested in learning how cells form or in creating synthetic cells.

Xianrui Cheng, PhD, a postdoctoral scholar, spotted the surprising behavior while performing experiments with frog egg cytoplasmic extracts consisting of the liquid contents of thousands of egg cells, as well as the nuclei — the organelles that normally serve as a cell's command center.

"Initially, we were looking at a cell death signal spreading through extract in a long thin tube. And I noticed that a segment-like structure started to appear," Cheng said.

After about 30 minutes, he saw that the nuclei were spaced evenly apart and boundaries had formed between them, resulting in the appearance of "sausage links" along the length of the tube.



The unscrambling of frog egg cytoplasmic extract is shown from left to right. Microtubules (green), endoplasmic reticulum (red) and nuclei (blue) rearrange to form cell-like compartments.

Out of curiosity, Cheng examined samples of the cytoplasmic extract on cover slips through a microscope. He was shocked to see distinct compartments that resembled a sheet of cells.

"If you take the cytoplasm of the frog egg — note that the cytoplasm has been homogenized, so whatever spatial structure that was there has been completely disrupted — and just let it sit at room temperature, it will reorganize itself and form small cell-like units. That's pretty amazing," Cheng said.

To understand how this reorganization happens, Cheng added chemicals to disrupt the cytoskeleton, a network of protein filaments that extends throughout the cytoplasm. These tests revealed that microtubules, cytoskeletal filaments that provide structural support to cells, were required for compartments to form. Similar experiments disrupting motor proteins revealed that dynein, a protein that transports cargo along microtubules, was also required for proper microtubule localization.

These cell-like compartments not only looked like cells; they divided like them too. The egg extract that the researchers used when they identified compartment formation contained a chemical that prevented the cells from entering the cell cycle. When this chemical was removed and sperm nuclei were added, the egg extract formed compartments that divided into smaller and smaller compartments.

Cheng and Ferrell shared these findings in an article published in the Nov. 1 issue of *Science*.

Their research suggests that the frog egg cytoplasm has the innate ability to generate the basic spatial organization of the cell and even has some of its functions. An open question, however, is what role this phenomenon plays in the normal physiology of the egg.

Such self-organization behaviors may be prevalent throughout biology. In the developing fruit fly embryo, thousands of nuclei initially share a common cytoplasm but ultimately form distinct cells and an organized body plan. Cells reorganize during mitosis, when structures break down and a single cell divides into two intact daughter cells.

As Cheng realized, there's more to the cytoplasm than it seems at first glance. — JACK J. LEE

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What's your type?

SCIENTISTS LAY OUT THE DIFFERENT WAYS WE AGE

Everyone has a type — and we're not talking about romance. We all have an aging type. As we get older, things start to falter, physically and molecularly, and it's different for everyone. Michael Snyder, PhD, professor and chair of genetics, and a team of researchers gathered data from 43 individuals over two or more years showing that these differences tend to align with one of four categories: metabolic, immune, hepatic (liver) and nephrotic (kidney). They call them "ageotypes." It's not something you can figure out on your own — pinpointing an ageotype takes massive amounts of data and continual measurements of biological samples, such as blood, stool and saliva.

"What happens to an individual as they age? No one's ever looked at the same person in detail over time," said Snyder, the Stanford W. Ascherman, MD, FACS, Professor in Genetics.

Ageotypes, which were described in a paper published Jan. 13 in *Nature Medicine*, show the biological pathways along which someone is showing signs of aging — such as spikes in molecules associated with disease. People with an immune ageotype, for instance, are more likely to generate higher levels of inflammatory markers or develop immune-related diseases as they age. A metabolic ager, however, may have a higher risk of heart disease from such conditions as obesity and diabetes.

But ageotypes aren't mutually exclusive. An immune ager could also be a metabolic ager, or some unlucky folks could be all four. On the bright side, the rate at which we age is amenable to change, regardless of ageotype. Some participants in the study showed that lifestyle changes could slow the growth of their ageotype markers. People who lost weight or changed their diet, for example, saw decreases in their levels of hemoglobin A1c, a measure of blood sugar levels.

"The ageotype is more than a label; it can help individuals zero in on health-risk factors and find the areas in which they're most likely to encounter problems down the line," Snyder said. "Most importantly, our study shows that it's possible to change the way you age for the better. We're starting to understand how that happens with behavior, but we'll need more participants and more measurements over time to fully flesh it out." — HANAE ARMITAGE