UCSF MAGAZINE

Summer 2023

Inside the Distressed **Teen Brain**

Rethinking treatment for adolescent depression

Contents

COVER: TIM MCDONAGH; TOP LEFT PHOTO: WALTER ZARNOWITZ; CENTER PHOTO: NOAH BERGER; BOTTOM LEFT ILLUSTRATION: SCOTT BAKAL; TOP RIGHT ILLUSTRATION: GIULIO BONASERA

The advent of cheap, easy-to-use blood tests for Alzheimer's disease has the potential to revolutionize diagnosis and treatment. But it also raises difficult questions that the field is only beginning to consider.

DEPARTMENTS

Alleviating Adolescent Anguish

American teens are in trouble.

Over the past decade, adolescent mental health distress in this country has skyrocketed. As you will read in our cover story, in 2021, almost half of teenagers reported feeling persistently sad or hopeless – up from 1 in 4 in 2011. Suicide rates have also climbed sharply. Compounding the crisis is a dearth of mental health specialists.

Seeking a way to help the many young people in need, UCSF child and adolescent psychiatrist Tony Yang turned to a surprisingly untapped resource: the teen brain.

Research by Tony Yang and others has begun to reveal how depression takes root in a teenage brain. Yang and Olga Tymofiyeva are leading UCSF's Brain Change study.

Tony, who is also a neuroscientist, was one of the first experts to research the neurobiology of teen depression by imaging young people's brains. His findings have informed a new way to treat the condition tailored to teens – one that draws from mindfulness meditation, yoga, and psychotherapy. What's more, teachers or counselors could administer it in schools.

If you are the parent, grandparent, aunt, uncle, or friend of a struggling teen, I hope you will read this story to better understand teens' distress and how they might build resilience.

The work of Tony and two colleagues – former fellow Eva Henje and imaging scientist Olga Tymofiyeva – exemplifies UCSF's vision for mental health. We are eliminating the boundaries that have long separated psychiatry from the neurosciences, allowing us to accelerate our understanding of the brain and reduce the stigma of seeking treatment. UCSF embarked on this goal after the founding of the Weill Institute for Neurosciences in 2016 and achieved another milestone last year with the opening of the Nancy Friend Pritzker Psychiatry Building. This one-of-a-kind treatment center also serves as a hub for collaboration between psychiatrists, neurologists, neurosurgeons, and other specialists.

We still have a long way to go to alleviate the mental health problems that devastate so many families. But the innovation and compassion of scientists like Tony, Eva, Olga, and others across UCSF give me confidence that we will get there.

Sam Hawgood, MBBS
Chancellor
Arthur and Toni Rembe Rock Distinguished Professor

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PHOTO: WALTER ZARNOWITZ

Five Questions for Heather Hervey-Jumper

Heather Hervey-Jumper, MD, became director of UCSF's Program in Medical Education for the Urban Underserved (PRIME-US) last summer to do work that inspires and sustains her.

By Katherine Conrad

Why PRIME-US?
Delivering health care to everyone has always been near and dear to my heart. When I heard that UCSF offered a specialized curriculum to teach medical students how to care for the urban underserved, I said, "That's my home."

What makes PRIME unique?
Medical schools traditionally taught facts. When I was a student, I learned that Black and brown people are more likely than white people to have asthma. But nobody said why. You're left to ask, "Is it genetic? Do I have bad lungs because I'm Black?" PRIME gives context: People of color often live in formerly redlined neighborhoods that have more air pollution, fewer parks, and poorly built houses – all contributing to higher asthma rates.

PRIME empowers students to change structural barriers and care for marginalized people through community partnerships, policy, and legislation. Our graduates become leaders for change within medical systems and on national platforms.

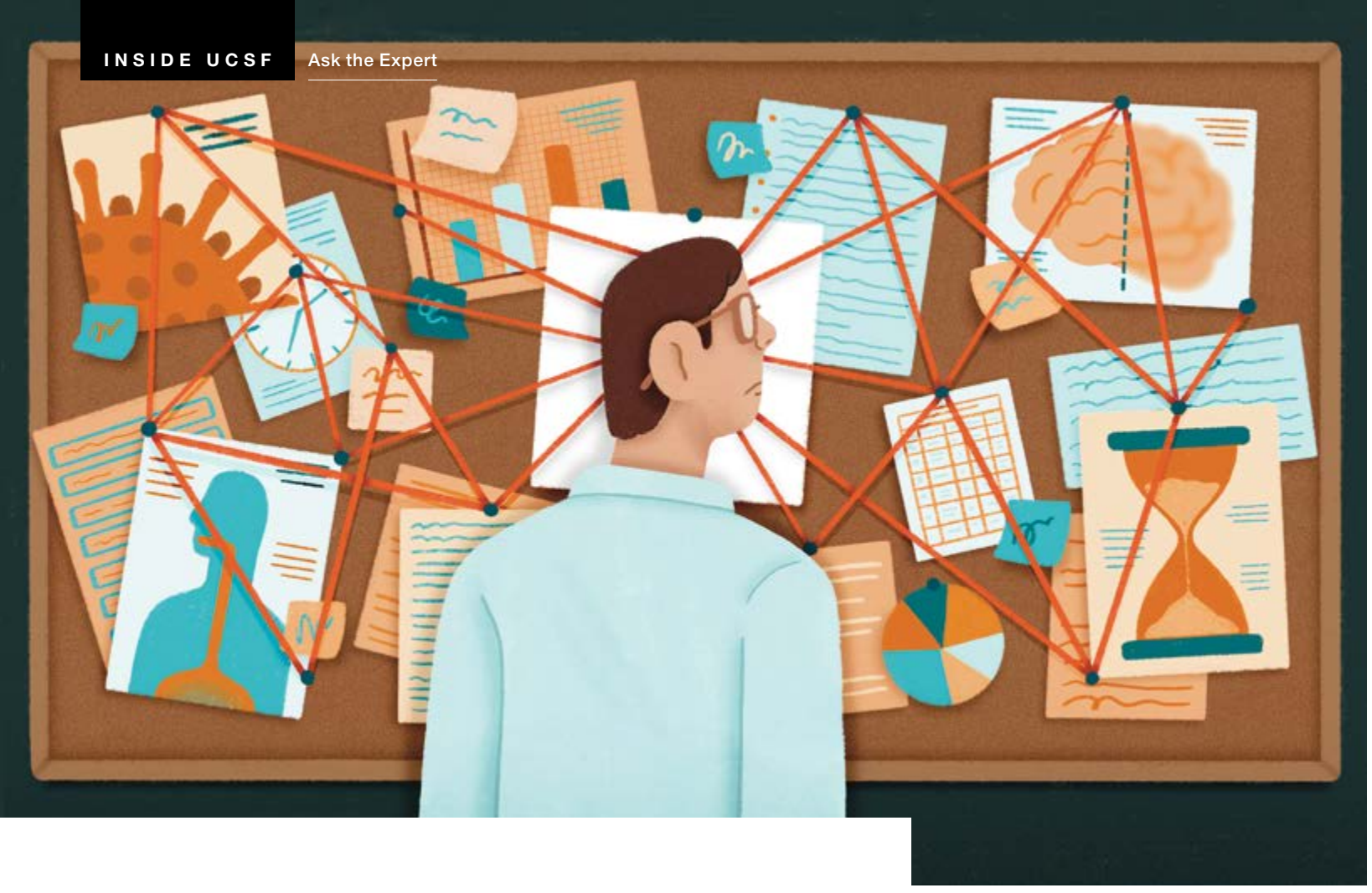
Fun fact:
Her family has pet goats. "We use them as lawnmowers!"

PHOTO: MARCO SANCHEZ

What advice do you give students?
Communities already have trusted leaders. Find them, work with them, let them tell you what they need and support that.

Why can't many San Franciscans get the care they need?
Wealth speaks powerfully. Homeowners will block a methadone clinic to treat opioid addiction because they fear it will hurt property values. We teach our students to provide awareness and evidence: "Hey, a methadone clinic improves your neighborhood because it offers recovery, employment, and hope."

What tools will the next generation of physicians need?
A deep understanding of the history of the communities they're serving. Respect for Indigenous and other healing practices so physicians can work synergistically with patients. Empowerment to enact change on a political level to improve access to care. And openness to how new tools, like artificial intelligence, can bridge gaps between haves and have-nots.



What's New in the Search for a **Long COVID** Cure?

By George Spencer

UCSF infectious disease specialist Michael Peluso, MD, who co-leads one of the world's oldest studies of long COVID, discusses the condition's mysteries. "There is no smoking gun," he says. "If that were the case, we would have figured this out two years ago."

What exactly is long COVID?

It refers to unexplained symptoms that are new or worse since someone had acute COVID and that are not attributable to other causes. They persist for at least three months after COVID's onset and impact a person's quality of life. Between 15 million and 30 million Americans may have it.

But there is not just one long COVID syndrome. Some people have profound neurocognitive symptoms, including difficulty concentrating. Others have cardiopulmonary symptoms that reduce their capacity to exercise. Others have disorders in their autonomic nervous system, with unexplained swings in their heart rate or blood pressure. And these categories are not monolithic. People can have symptoms across the categories.

I don't think anybody believes a single pathological mechanism causes all cases of long COVID. It's likely that different types of long COVID have different drivers.

Who is most at risk?

Long COVID can happen to anyone, but women are at higher risk than men. No one knows why. We've just started a collaboration to specifically address that question. People who are older or middle-aged are also more affected, as are those with pre-existing conditions like diabetes or obesity.

I tell my patients that outside of not getting COVID, the most important thing people can do to reduce their risk of developing long COVID is to be up to date on their vaccinations. An open question – and it's an important question – is whether treatment with an antiviral during the acute phase of

ILLUSTRATION: PAIGE STAMPATORI

the infection will lower someone's likelihood of developing long COVID. Another question is whether reinfections, which many people are now experiencing, will increase the risk of long COVID.

Before COVID, you led a UCSF study into how HIV infection persists. A few weeks after COVID began, you and your team turned on a dime to create a study called LIINC (Long-term Impact of Infection with Novel Coronavirus). Why?

We saw that many scientists were focused on acute infection because it was so scary, but not many were paying attention to what would happen next. When we set up LIINC, long COVID wasn't even a known entity. It felt like we were venturing into the unknown. We began to study post-COVID immunology, but we knew that many other infections have postinfectious complications, so we made sure to ask our study participants about that.

LIINC was one of the world's first studies of long COVID. We are now deeply involved in national research efforts as well. We helped the NIH design and implement its Researching COVID to Enhance Recovery (RECOVER) initiative, and we're one of its study sites.

Is long COVID primarily a neurological disease?

Maybe. The nervous system could be responsible for a lot of long COVID symptoms, and neurological symptoms seem to be the ones that are talked about the most. Brain fog is one of the most significant and debilitating symptoms in some people. Since the beginning, we at LIINC have worked closely with other UCSF researchers who are specifically investigating brain fog. But there are many people with long COVID who do not have neurological symptoms. It seems that many different organ systems might be involved.

What are you learning about the underlying mechanisms of long COVID?

When LIINC began, early on we observed that people with long COVID had higher levels of inflammation. Some of our work has shown that people with heart symptoms or brain fog due to long COVID have higher levels of inflammation in their blood. Then we started exploring the causes of that inflammation. We found that many people with long COVID have "leaky gut," or higher levels of bits of gastrointestinal bacterial and fungal organisms elsewhere in their bodies. And those levels are directly related to higher amounts of inflammation in their blood.

We've also been interested in the relationship between long COVID and prior Epstein-Barr infection, because people with reactivation of that infection appear twice as likely to report having long COVID. And, interestingly, they seem to be more likely to have brain fog symptoms.

The hottest topic now is viral persistence. We suspect that inflammation can be driven by pieces of viral protein lingering in the body. We recently published a paper on people with brain fog or new depression or anxiety symptoms after COVID. It found they had COVID proteins in their blood months after they got COVID. That was a very surprising observation, because the virus that causes COVID is not supposed to persist. We are planning follow-up studies on this topic now.

How soon will we see treatments targeting the causes of long COVID?

Today, 100% of long COVID management targets symptoms, not underlying biological pathways. I'd like to speculate that sometime this year, there will be clinical trials targeting concerns like viral persistence or inflammation. I hope some lead quickly to answers and effective therapies that fix the underlying problem.

Do people still need to worry about COVID?

I continue to be extremely worried about it. I spend all my time interacting with people who were fine before they had COVID and are now debilitated. Many have lost their jobs; their relationships have been affected; they are struggling. Even with all the progress that has been made with vaccines and treatments, I am still worried. There's a real reckoning to be had between balancing the long-term consequences of getting COVID, which we are only beginning to understand, and everybody getting back to their normal lives. It's hard for me to say that something that still causes tens of thousands of new infections a week, and kills hundreds of people a week, and has all of these long-term effects, is in the background.

PHOTO: STEVE BABULJAK

Cellular 'Glue' Can Regenerate Tissues, Heal Wounds, Regrow Nerves

Researchers at UCSF have engineered molecules that act like "cellular glue," allowing them to direct, in a precise fashion, how cells bond with each other. The discovery represents a major step toward building tissues and organs, a long-sought goal of regenerative medicine.

Adhesive molecules are found naturally throughout the body, holding its tens of trillions of cells together in highly organized patterns. They form structures, create neuronal circuits, and guide immune cells to their targets. Adhesion also facilitates communication between cells to keep the body functioning as a self-regulating whole.

In a new study, researchers engineered cells containing customized adhesion molecules that bonded with specific partner cells in predictable ways to form complex multicellular ensembles. "We were able to engineer cells in a manner that allows us to control which cells they interact with and also to control the nature of that interaction," says senior author Wendell Lim, PhD (above), the Byers Distinguished Professor of Cellular and Molecular Pharmacology and director of UCSF's Cell Design Institute.

Cardiac anesthesiologist Charlene Blake, MD, PhD (left); surgeon Amy Fiedler, MD (second from right); and perfusionist Ashley Risso, MS (right), pose with patient Fatou Gaye.

All-Women Heart Transplant Team Makes History

In December, UCSF cardiac surgeon Amy Fiedler, MD, led what is likely the first all-women team to perform a heart transplant. It's a milestone for the 56-year-old field, in which women are heavily underrepresented.

Fiedler didn't notice that everyone in the room was female – including the nurses, the surgical trainee, and even the patient – until after the five-hour operation. Surgical teams are assigned randomly, so that possibility was remote. "Never thought I'd see the day," she posted on Twitter. "The future is bright!!!"

It "makes me feel so happy and proud that women can and do get it all done," the patient, Fatou Gaye, told the *San Francisco Chronicle*. Less than a month after the surgery, she said, she was walking without pain or shortness of breath.

Fiedler attributes the growing diversity of UCSF's surgery faculty and staff to the leadership of department chair Julie Ann Sosa, MD, and former chair Nancy Ascher, MD, PhD, the first woman to transplant a liver. "We've come a long way," says Fiedler, who is one of only about 20 female heart transplant surgeons nationwide. "It means so much to be able to show the next generation of clinicians, 'You can do this.'"

How Sleep Ups the Score

When the Golden State Warriors' Steph Curry makes a free throw, his brain draws on motor memory. Now, researchers at UCSF have shown how this type of memory is consolidated during sleep, while the brain processes the day's learnings to make the physical act of doing something subconscious.

The study shows that the brain does this by reviewing the trials and errors of a given action. In the basketball analogy, that means sorting through all the free throws Curry has ever shot, then weeding out the memories of all the actions except those that hit the mark or that the brain decided were "good enough." The result is the ability to make a free throw with a high degree of accuracy without having to think about the physical movements involved.

"Even elite athletes make errors, and that's what makes the game interesting," says Karunesh Ganguly, MD, PhD, a professor of neurology and member of the UCSF Weill Institute for Neurosciences. "Motor memory isn't about perfect performance. It's about predictable errors and predictable successes. As long as the errors are stable from day to day, the brain says, 'Let's just lock this memory in.'"

TOP PHOTO: RAYMOND IBALE; BOTTOM PHOTO: CHARLENE BLAKE; BASKETBALL HOOP: GEARSTD

Machine Learning Enables Diagnosis of Sepsis, an Elusive Global Killer

Sepsis, an overreaction of the immune system in response to an infection, causes an estimated 20% of deaths globally and as many as 20% to 50% of U.S. hospital deaths each year. Despite its prevalence and severity, the condition is difficult to diagnose and treat effectively.

The disease can cause decreased blood flow to vital organs, inflammation throughout the body, and abnormal blood clotting. If sepsis isn't recognized and treated quickly, it can lead to shock, organ failure, and death. But it can be hard to identify what pathogen is causing sepsis, or whether the infection is in the bloodstream or elsewhere in the body. And in many patients with symptoms that resemble sepsis, it can be challenging to determine whether they truly have an infection at all.

Now, researchers at UCSF, the Chan Zuckerberg Biohub, and the Chan Zuckerberg Initiative have developed a new diagnostic method that can identify and predict sepsis. The approach applies machine learning to genomic data from a pathogen and its host to generate surprisingly accurate diagnostics. The method has the potential to far exceed current capabilities.

The new method was able to identify

99%

of confirmed bacterial sepsis cases and

92%

of confirmed viral sepsis cases. It could predict sepsis in

74%

of clinically suspected cases.

Who Needs the 'Love Hormone' Anyway?

New research from scientists at UCSF and Stanford shows that the receptor for oxytocin, a hormone long considered essential to forming social bonds, may not play the critical role that scientists have assigned to it for the past 30 years.

The team found that prairie voles that were bred without oxytocin receptors showed the same monogamous behaviors related to mating, attachment, and parenting as regular voles did. In addition, females without oxytocin receptors gave birth and produced milk, though in smaller quantities, similarly to ordinary female voles.

The results indicate that the biology underlying pair bonding and parenting isn't dictated purely by the receptors for oxytocin, sometimes called the "love hormone." Instead, oxytocin is likely just one part of a much more complex genetic program.

Prairie voles are one of the few mammalian species known to form lifelong monogamous relationships.

ILLUSTRATION: CATERINA_K

Recommended:

Books, Videos, & Podcasts

READ

The Truth About Dietary Supplements

Drawing on her decades of research and clinical experience, Mahtab Jafari, PharmD '94, a professor of pharmaceutical sciences at UC Irvine, sheds light on the largely unregulated supplement industry and empowers readers to make choices informed by science.

WATCH

Invisible Corps

There's only one uniformed service in the world dedicated to public health: the Commissioned Corps of the U.S. Public Health Service. This PBS documentary explores its history and highlights some its officers, including former U.S. Surgeon General Richard Carmona, MD '79, MPH, and former Chief Pharmacist Officer Pamela Schweitzer, PharmD '87. Stream it on pbs.org.

LISTEN

Brains and Braggadocio

As part of its miniseries on Black excellence in STEM, Carry the One Radio interviewed UCSF's Akinyemi Oni-Orisan, PharmD, PhD. The assistant professor of clinical pharmacy shares how he's improving cardiovascular care for everyone and how he inspires confidence in himself and his students. Find it on your favorite podcast forum.

Which Skin Care Products Do We Really Need?

Skin care is big business – just ask the multibillion-dollar beauty industry. But does it truly take a cabinet full of pricey products to keep our skin healthy?

By Christina Hernandez Sherwood

From cleansers to creams and serums to sunscreens, the skin care aisle is bursting with products that promise to make our skin look brighter, softer, younger, *better*. But which products are must-haves, and which are unnecessary? Should you shell out extra cash for "clean" cosmetics? And is sunscreen really *that* important?

We asked a trio of UCSF dermatologists our burning questions about skin care to find out which products should earn a spot on our shopping lists.

MYTH #1: I need to follow a complex – and expensive – skin care routine to keep my skin healthy as I age.

Actually, a simple drugstore moisturizer is the most important product, aside from sun protection, in your anti-aging skin care routine, says Katrina Abuabara, MD, an associate professor of dermatology at UCSF with an interest in eczema. Moisturizer helps protect the skin barrier, a pivotal function of our body's largest organ.

As we get older and the immune cells in our skin amass more exposure to toxins, allergens, and pollutants, our skin's ability to function as a barrier declines, Abuabara says. This can cause low-grade skin inflammation, with symptoms including redness and dryness. Inflamed immune cells from the skin may spread throughout the body, causing systemic inflammation, which can lead to a host of serious health problems.

For instance, patients with moderate to severe eczema, a skin condition characterized by a red and itchy rash, have higher rates of cardiovascular disease. Last year, Abuabara was the lead author of a study showing that adult patients with eczema have a 27% increased risk of dementia.

For older adults and those with dry skin, one of the best ways to prevent skin inflammation is to apply moisturizer. Experts at UCSF and elsewhere are studying whether moisturizer use could actually ease inflammation-related problems beyond the skin. Peter Elias, MD '67, UCSF dermatology professor emeritus, found that applying Vaseline petroleum jelly to mice reduced the levels of inflammation in their blood. A small study by Elias and other researchers suggested the same might be true of humans.

"I don't think we're going to cure dementia with Vaseline," Abuabara says. "But putting moisturizer on older adults may help as part of a general strategy – and it's so low cost and easy and safe that it is something people could consider as part of elder care."

So, using moisturizer is a good idea, but how does one choose from the countless products available? The products with the most moisturizing power are ointments like Vaseline and oils, Abuabara says. Creams are the next most moisturizing, then lotions and gels. "It just depends on how dry you are and what type of product you prefer," she says. "Everyone's a little different."

MYTH #2: If I wear sunscreen all the time, I won't get the vitamin D that I need.

While it's true that 90% of our vitamin D comes from sun exposure, that's hardly a get-out-of-jail-free card when it comes to sun protection, says Lindy Fox, MD, a UCSF professor of dermatology who cares for hospitalized patients with complex skin conditions. Even with a sunscreen routine, most healthy people get enough unintended sun exposure that they don't need a vitamin D supplement.

Experimental research – studies with a control group and an experimental group – has shown that using sunscreen reduces vitamin D absorption, Fox says. But observational studies – in which researchers observe what participants do naturally – indicate that sun protection doesn't cause people's vitamin D levels to drop.

ILLUSTRATION: FARAH HAMADE

WHAT SHOULDN'T BE ON THE INGREDIENT LIST?

Watch out for substances with the potential to cause irritation or skin reactions, such as fragrances, essential oils, and certain preservatives like methylisothiazolinone and propylene glycol.

That might be because most people don't use enough sunscreen. One ounce – about the size of a shot glass – is the amount of sunscreen required to cover the entire body once, Fox says. And if you're swimming and sweating, you should reapply sunscreen every two hours. That means a typical adult on a beach vacation should use up an entire three-ounce bottle of sunscreen in a single day.

Even if you spend most of the day inside, UVA rays penetrate your home, office, and car windows unless a UVA-specific blocker has been added to the glass.

Unprotected sun exposure is a known risk factor for skin cancer, so Fox says sun protection is a must for everyone. "You should be using sunscreen every day, just like you brush your teeth," she says. "Sunscreen should go on sun-exposed areas, including, for ultimate sun protection, your face, your chest, your hands, your arms." (And don't forget to reapply it before a lunchtime walk.)

Supplementing a sunscreen routine with sun-protective clothing, such as rash guards and wide-brimmed hats, is also a good idea.

MYTH #3: My dark skin protects me from skin cancer, so I can skip sunscreen. Sorry, but people with darker skin tones still need sun protection – though perhaps not for the same reasons as those with lighter skin, says assistant professor of dermatology Jenna Lester, MD, who directs UCSF's Skin of Color Program.

It's true that melanin, a natural pigment that gives color to skin and is more abundant in darker-skinned people, is protective against skin cancer, Lester says. That's probably why melanoma is less common in people with darker skin, though it is more deadly in those who are diagnosed with it.

Based on what dermatologists know today, sunscreen use does not prevent melanoma in Black patients. But focusing sun protection education largely on skin cancer prevention ignores the reasons why people of color should wear sunscreen, Lester says. "We center the concerns of white patients in the dermatology experience," she says. "We don't really talk about sunscreen as much when we're talking about discoloration or uneven skin tone or the visible signs of sun damage in someone with dark skin."

Regular sunscreen use can help prevent a host of pigmentary disorders, including melasma, a condition in which darker patches or spots appear on the face.

People with darker skin are less likely to develop wrinkles caused by sun exposure, Lester says, but they can develop an uneven skin tone. "A daily sunscreen practice can help prevent that from ever being a problem," she says.

MYTH #4: "Clean," "natural," or organic skin care products are better. Nope. In fact, products touted as "clean," "natural," or organic are often worse for the skin. "People use products they think are better because they're called 'clean,'" Fox says. "They end up coming to us with sick skin full of rashes, allergies, and other problems."

The ingredients in these products tend not to be well studied, Fox says. And cosmetics don't have to be approved by the U.S. Food and Drug Administration before being sold. "The problem with the clean beauty movement," she says, "is that there's no definition of 'clean.'"

Here's how this dermatologist defines a good skin care product: It contains ingredients that are good for the skin, that have scientifically proven efficacy, and that won't cause allergies or irritations. Some of these include retinoids for anti-aging, niacinamide for hydrating and restoring the skin barrier, ceramides for locking in moisture, and squalane, a skin softener that improves elasticity and reduces visible signs of aging.

ILLUSTRATION: CHRIS GASH

Making Sense of Scents

Knowing how our sense of smell works – what makes jasmine a delight and rotting fish abhorrent – has long baffled scientists. Now, researchers at UCSF have created the first molecular-level, 3D picture of how an odor molecule activates a human odorant receptor, a crucial step in deciphering olfaction. The findings are poised to reignite interest in the science of smell and hold implications for the fragrance industry, food science, and other manufacturing businesses.

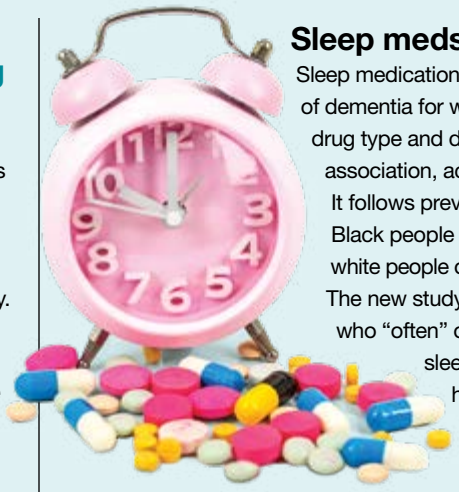
Breakthroughs and Other Buzz

Can lymph nodes increase tumor-tackling cells? Only a small fraction of solid tumors respond to immunotherapy treatments, but new findings by UCSF and the Gladstone Institutes suggest that leaving lymph nodes intact until after these treatments could boost their efficacy.

Dentistry and medicine unite! Oral health impacts conditions ranging from heart disease to preterm birth, yet it's often hard for clinicians to see a picture of their patients' health that encompasses dental as well as medical issues. Now, UCSF providers will have a better view: The university has become the first academic health system in the western U.S. to integrate electronic health records across its medical and dental services.

No. 1 in NIH funding: UCSF received the most National Institutes of Health funding of any public institution for the 16th consecutive year. The university's $823 million total for FY 2022 set a record for NIH funding to a public university.

Sugar tax success: Taxes on sugary drinks reduce the risk of gestational diabetes and unhealthy weight gain in pregnant women, according to a UCSF study of more than 5 million women. Sugar-sweetened beverages are associated with a higher risk of obesity, type 2 diabetes, and cardiovascular disease.



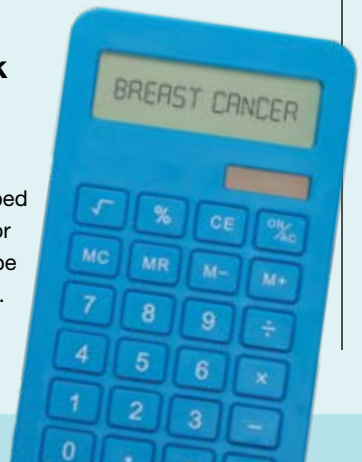
Sleep meds and dementia: Sleep medications may increase the risk of dementia for white people, though the drug type and dosage may explain the association, according to a UCSF study. It follows previous work showing that Black people have a higher likelihood than white people of developing Alzheimer's. The new study found that white people who "often" or "almost always" used sleep medications had a 79% higher chance of developing dementia than those who "rarely" or "never" did so.

Start heart health early: **A new UCSF-led study showed that people who develop cardiovascular disease when young could develop memory and thinking problems in middle age. The findings underscore the fact that everyone, including young adults, should strive for a heart-healthy lifestyle.**

Anti-smoking push = billions saved: Over the past 30 years, the California Tobacco Control Program has helped Californians save $816 billion in health care costs, according to a UCSF study. For every dollar the state spent on smoking control, health care costs fell by $231.

Where women lost abortion access: **One-third of U.S. women now face excessive travel times to obtain an abortion, according to researchers at UCSF, Harvard, and Boston University. Their geospatial analysis is one of the first to model the effects of the Supreme Court's *Dobbs v. Jackson* decision.**

New breast cancer risk calculator: Determining who will develop breast cancer is still a major challenge for the medical community. A new app, co-developed by UCSF, helps calculate the risk for women whose breast cancer may be undiagnosed by regular screenings.



Eyes on diabetes: A new collaboration between UCSF, UC Davis, UCLA, and UC San Diego will expand remote eye screenings to prevent blindness and other vision complications due to diabetes, particularly in underserved communities.

Can the ER improve public health? UCSF researchers found that distributing COVID-19 vaccine information in English and Spanish in emergency departments increased vaccine acceptance, especially among Latinos and people without a primary care physician. The finding lays the groundwork for delivering other public health information to vulnerable populations in ERs.

A pill to curb binge drinking: Men who drink more than four alcoholic drinks in a sitting, and women who drink more than three, face a high risk of alcohol-related illnesses and injuries. A recent UCSF study suggested that using the decades-old medicine naltrexone could reduce the amount of alcohol individuals consume.

Magic mushrooms as an antidepressant: Psilocybin, the hallucinogenic compound in "magic mushrooms," fosters better brain connections in depressed people than in those without depression, freeing them up from long-held patterns of rumination and excessive self-focus, according to a study by UCSF and Imperial College London.

TOOTHBRUSH: ISTOCK/BEDO; ALARM CLOCK: ISTOCK/ PIMPIC; CALCULATOR: ISTOCK/ VLADIMIR SUKHACHEV

The Case of the Brain-Eating Amoeba

After diagnosing a middle-aged man with an incredibly rare and almost always fatal infection, a medical team led by UCSF fellow Natasha Spottiswoode raced to find a treatment that could save his life.

By Jill Sakai

ILLUSTRATION: ELEANOR DAVIS

IN THE SUMMER OF 2021, AN OTHERWISE healthy man in his mid-50s had a sudden, unexplained seizure. After an MRI at his local hospital revealed a lesion on his brain, he was transferred to UCSF Medical Center for specialty care.

A biopsy ruled out most of the usual suspects, including cancer, bacterial or fungal infections, and tuberculosis. Then the UCSF team noticed a curious pattern in the biopsied tissue that made them think the problem might be an amoeba.

Single-celled amoebas commonly inhabit soil and water; occasionally, they can enter a human body through the nose, mouth, or skin and migrate to the brain. This happens so infrequently, though, that few medical centers in the U.S. are equipped to test for an amoeba infection. The UCSF team sent a sample of the biopsy to a specialized lab that confirmed their hunch: The man's brain had been infiltrated by the "brain-eating" amoeba *Balamuthia mandrillaris*.

Such infections are nearly always fatal. And for the few *Balamuthia* survivors, there's no clear evidence of what saved them. "It's not a disease with a great deal of good data because it's so rare and so deadly," says Natasha Spottiswoode, MD, PhD, a UCSF infectious diseases fellow who helped care for the patient.

After consulting with the U.S. Centers for Disease Control and Prevention, the UCSF team started the patient on an intensive – and highly toxic – regimen of antibacterial, antiparasitic, and antifungal drugs based on what had been given to previous *Balamuthia* patients. But soon after, the man's kidneys began to fail, and his blood sugar levels and white blood cell counts dropped dangerously low. So the team stopped giving him the most noxious medications. His brain lesions multiplied and grew as the amoebic infection spread.

In an urgent search for a better treatment, Spottiswoode scoured the medical literature. One paper in particular caught her eye: a 2018 report by UCSF researchers who, after another patient died from a *Balamuthia* infection, had been determined to find a cure. They screened more than 2,000 drugs looking for something that could beat the amoeba. Their lead candidate: nitroxoline.

The drug is prescribed for urinary tract infections in some countries but isn't available in the U.S. However, the paper's senior author, Joe DeRisi, PhD, pointed Spottiswoode to a manufacturer in China. She immediately contacted the company. "They were incredibly kind and helpful," she says, and supplied the nitroxoline for free. After getting approval from the U.S. Food and Drug Administration for emergency use, her team had a potentially lifesaving treatment in hand.

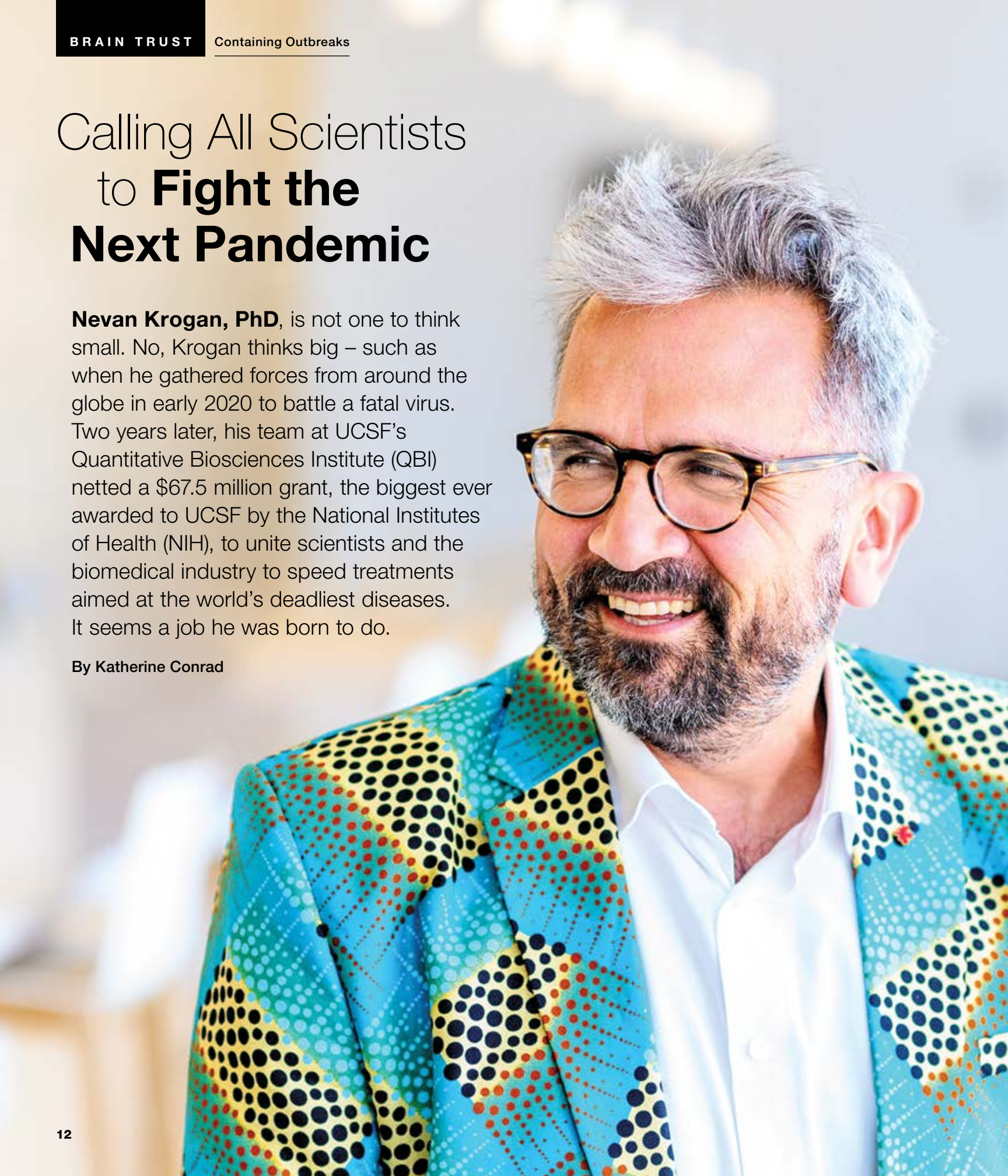
The patient's lesions began to shrink after he was on nitroxoline for one week, Spottiswoode recalls. After seven weeks, the team could see that the infection was clearing.

The patient is now home, and Spottiswoode's team continues to monitor his progress. "There's no road map," she says. "He's the first person to have been successfully treated with this drug for this condition – ever."

Calling All Scientists to **Fight the Next Pandemic**

Nevan Krogan, PhD, is not one to think small. No, Krogan thinks big – such as when he gathered forces from around the globe in early 2020 to battle a fatal virus. Two years later, his team at UCSF's Quantitative Biosciences Institute (QBI) netted a $67.5 million grant, the biggest ever awarded to UCSF by the National Institutes of Health (NIH), to unite scientists and the biomedical industry to speed treatments aimed at the world's deadliest diseases. It seems a job he was born to do.

By Katherine Conrad



Why do you think QBI was selected for this huge challenge?
We are connectors. We connect different institutions at UCSF, around the United States, around the world. We connect governmental agencies with scientists. We connect scientists and nonscientists.

Is that unique?
Incredibly. Science is often very siloed, as are scientists. If you look at UCSF, there's the cancer center, the neurodegeneration center, etc. But QBI shows what happens when you bring scientists together from different disciplines, when you use disease-agnostic technology to facilitate these connections. That's where the big breakthroughs happen.

For example?
When the pandemic hit, we immediately looked at our worldwide map and said, "Who can we work with?" We had already established trust at the Institut Pasteur in Paris and at New York's Mount Sinai Hospital, which has one of the best microbiology departments in the U.S. We turned to them, and away we went.

That is unusual?
Yes. We could move fast because we had built this worldwide network. Thank God we had a relationship with the Institut Pasteur, because they had the virus growing in a BSL-3 [biosafety level 3 laboratory] early in the pandemic. We didn't have it here in San Francisco until later, and it was crucial for research.

All the work that we accomplished, as well as the NIH grant – none of that would have happened if we hadn't laid the tracks before the pandemic with Institut Pasteur.

Seems like making connections comes easily to you. Is that a personality trait?
I think so. In science, I'm in the business of making connections between proteins. When QBI came to fruition, I hired Jacqueline Fabius as the COO. She is not a scientist; she worked at the United Nations. People said to me, "What? The UN?" I said, "We need somebody who can help facilitate relationships around the world."

How did these connections help during the early days of the pandemic?
We were the first group in the world to clone all the genes for SARS-CoV-2, about 30 of them, in January 2020. We distributed them to over 400 labs in 40 countries in a couple of weeks, which helped expedite research on the novel coronavirus.

Next, we looked at what human proteins were touching the viral proteins, because the virus needs our proteins to live, to replicate, and to infect us. We identified about 300 proteins out of 20,000 human proteins that the virus was hijacking.

Then, in efforts led by QBI investigators Kevan Shokat and Brian Shoichet, we worked to find drugs already in clinical trials that targeted those proteins. We identified a whole slew, but two stood out: zotatifin and plitidepsin. Both are now in clinical trials to treat COVID-19. They're anti-cancer drugs, by the way.

Did that surprise you?
No, it didn't, because it comes back to science being siloed. When you look across disease areas, you see commonalities. It's the same genes being mutated in cancer that SARS-CoV-2 is hijacking. It's the same genes being mutated in autism that Zika is hijacking. It makes sense.

The NIH grant covers several deadly viral families – including Zika, measles, hemorrhagic fevers, and Ebola – all with pandemic potential. Will your team develop treatments?
Yes. During our COVID work, we built up an international collaboration among over 300 laboratories. We leveraged this network to include virologists with specialties in those diseases who are in London, New York, Paris. Half of the 43 labs on the grant are from QBI, and the other half are spread around the world.

Will this project revolutionize traditional drug development?
Going back to silos, I believe that this will force academics to think more about how their discoveries can be translated into treatments. I hope that this work will be revolutionary, that it will show us how to use our tools more effectively for drug discovery and show us all the value of partnering between academia and industry. That'll have a much more profound impact than just targeting SARS-CoV-2. During the pandemic, a lot of people realized the value of relationships with pharmaceutical companies.

Before COVID, it wasn't friendly?
Twenty years ago, not so much. During the pandemic, people threw all the barriers out the window – and look how fast the world moved. We didn't even know about COVID a little more than three years ago. Now, we've got vaccines. We've got drugs. That's unheard of in the biomedical world. Usually, it takes decades. It happened because everybody was collaborating – scientists, universities, pharmaceutical firms.

Now, as the dust settles – if it is settling from this pandemic – the question is: Can we learn from these lessons? Why aren't we studying all diseases like this? Breast cancer, Parkinson's, Alzheimer's?

What do you think?
The vision was there before 2020. The pandemic was a huge tragedy. It was also a huge opportunity that we used for good. I truly believe that because of the pandemic, a couple of decades from now, we're going to have many more treatments for diseases.

Wow. That's because…?
We learned so much. The challenge is to make sure we implement the lessons going forward. Enough of us will. I believe the pandemic, in the long run, ironically, is going to save more lives than it cost.

Those are big words.
They are big words. We'll see if they're true.

Nevan Krogan, director of UCSF's QBI, was awarded the Legion of Honor, France's highest decoration, for forming an international research collaboration to study SARS-CoV-2 in the early days of the pandemic.

PHOTO: NOAH BERGER

CAN NEUROSCIENCE HELP STEM THE TIDE OF TEEN DEPRESSION?

A new treatment approach draws on research into the unique teenage brain.

By Ariel Bleicher Illustrations by Tim McDonagh

> **"THERE WAS JUST THIS VERY STRONG SENSE OF LONELINESS."**
> **-LILLIAN CARSON**

Lillian Carson was 11 when the fear struck. She had always been a sensitive child who tuned in to the feelings of animals and other people. But after her dad was diagnosed with cancer, she spiraled into worry and sleeplessness. "I would be up at night, huddled in the corner with my dog, and my sheets over my head, thinking someone was going to break through my window and get me," she remembers.

Her parents took her to therapy, which eased her anxiety for a while. "It was still prevalent in my life, but it wasn't something that stopped me from being a kid," Lillian, now 16, says. "Then the pandemic came, and that all changed pretty rapidly."

Lillian was about to graduate from middle school when the world went into lockdown. By then, her dad's cancer was in remission. She was dancing hip-hop and going to plays and art museums with her family. She had just experienced "some bad friend-group stuff" and was looking forward to high school. "I thought it would be a fresh slate for me," she says.

Instead, she found herself alone in her room most days, hunched over her laptop or on her phone. "I had absolutely no connections, no friends to talk to, no one really to hang out with," she says. "There was just this very strong sense of loneliness."

The fear returned with a vengeance. She stopped sleeping again. A mild chest injury morphed into a condition called amplified musculoskeletal pain syndrome, which can be brought on by psychological stress. "She had these bouts of intractable pain," recalls Lillian's mom, Beryle Chandler-Carson. "We were going to the ER in the middle of the night and seeing dozens of different medical specialists."

Meanwhile, getting a mental health appointment proved next to impossible. "There was nobody who could get you in unless it was online," Lillian says. And online therapy, in her opinion, was a bust. "It feels really hard to be yourself and be connected when it's on a screen," she explains.

Lillian is not alone in her suffering. Even before COVID-19, teen mental distress was spreading at an alarming clip. In 2011, 1 in 4 high schoolers felt persistently sad or hopeless, according to survey data from the U.S. Centers for Disease Control and Prevention. By 2019, the ratio had jumped to 1 in 3. In 2021, at the height of the pandemic, almost half of teens reported such feelings. Over the same decade, emergency room visits by children and young adults for anxiety, mood and eating disorders, and incidents of self-harm climbed sharply. Suicide rates soared.

"It's a problem that's been at a crisis level for years, and COVID just threw fuel on the fire," says Tony Yang, MD, PhD, a child and adolescent psychiatrist and neuroscientist at UC San Francisco. The tide of adolescent anguish spans geographic, economic, and racial and ethnic divides. And its causes are multifaceted and still poorly understood. Should we blame the rise of social media and cyberbullying? The decline in sleep, exercise, and good nutrition? The earlier onset of puberty? The political and climatic turmoil that has beset the world?

Making matters worse, most teens who need help can't get it. "There just aren't enough therapists who are trained to handle the huge demand of patients," Yang says. In California, more than half of counties have as few as one child and adolescent psychiatrist for every 100,000 children, and almost a third of counties have none. Even in San Francisco County, where youth mental health specialists are relatively plentiful, waitlists for therapy can be as long as a year.

In search of a solution, Yang turned to a resource that the field of psychiatry had long overlooked: the teenage brain. He was one of the first experts to study the underlying neurobiology of teen depression by imaging neural activity and connections. His research has helped uncover new insights into the condition and inspired an intervention, tailored for teens like Lillian, called Training for Awareness, Resilience, and Action (TARA).

The 12-week program – developed by Yang's former fellow Eva Henje, MD, PhD – draws from mindfulness meditation and yoga as well as more traditional forms of psychotherapy. Mindfulness practices, which originated in the Buddhist and Hindu traditions, cultivate the ability to observe experiences in the present moment without reaction or judgment. Mounting evidence shows that these practices can alleviate depression and anxiety and reduce relapses in adults. Yang is now leading studies of TARA with UCSF's Olga Tymofiyeva, PhD, to see whether the intervention can similarly benefit teens who can't get or may not need advanced professional care.

"The advantage of TARA is that it doesn't require a clinical psychology degree to deliver it," Yang says. "High school teachers and counselors could be trained to do it."

OF PUBERTY AND PLASTICITY

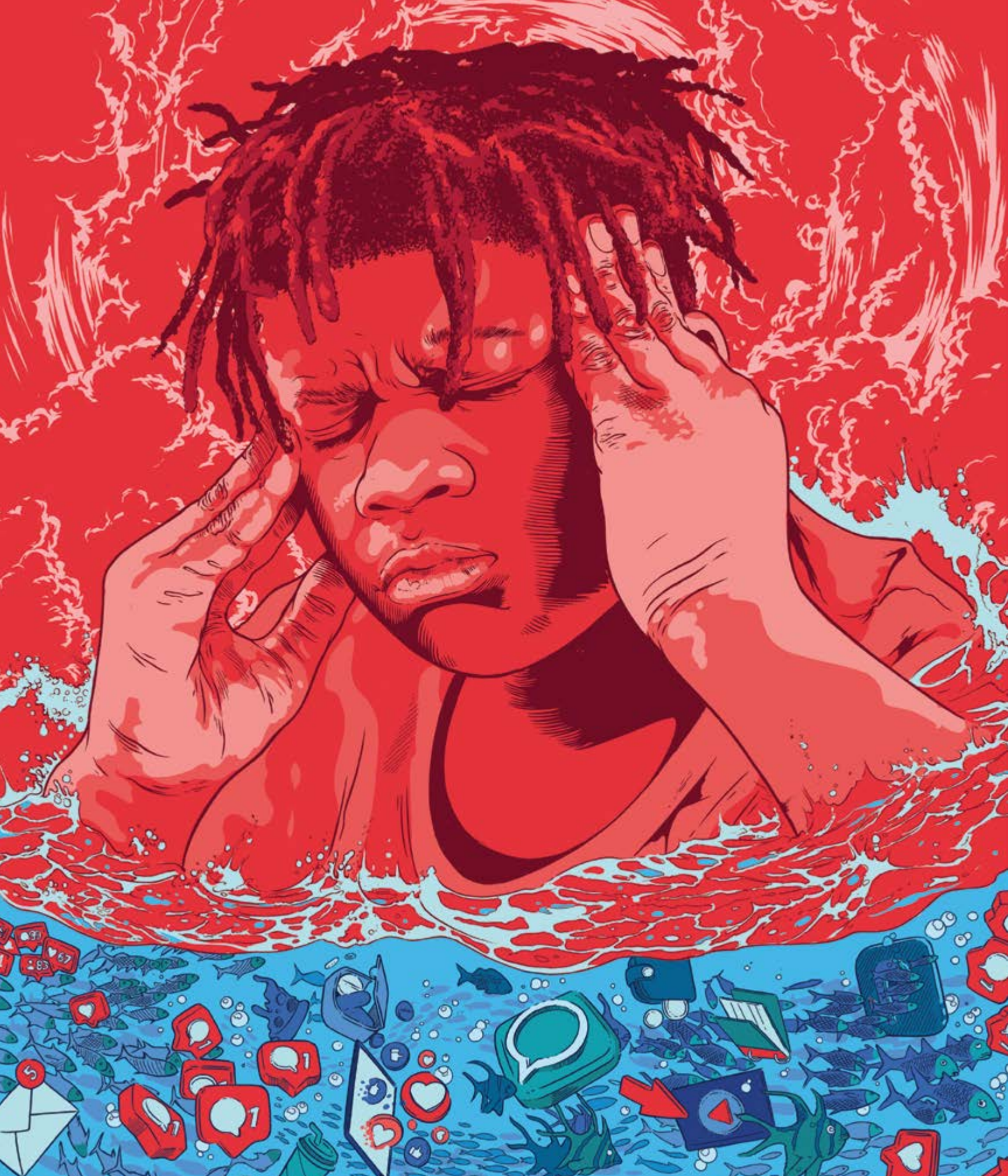
Adolescence is a tumultuous time for the human brain. Puberty ushers in a period of profuse neural rewiring that is surpassed in scale only during the first three years of life. Well-worn tracks between neurons strengthen, while idle paths are pruned away, allowing different parts of the brain to become more interconnected and specialized.

But this remodeling is not uniform. The most dramatic and rapid changes occur in the limbic system and other structures that drive emotions and respond to reward, novelty, and threat. By contrast, the prefrontal cortex – which carries out executive functions like reasoning, planning, and social interaction – matures slowly, until well into a person's 20s.

The roughly 10-year gap between the ripening of these two brain areas primes teens to act impulsively, take risks, and seek out the approval of peers. "It's why, when you're a teenager, you have a harder time exercising good judgement," Yang says. It's also why teens are particularly vulnerable to mood disorders like depression.

Although depression in teenagers shares many characteristics with adult depression, there are important differences. Most adults with depression are despondent; they shut down and turn inward. Depressed teens can be gloomy, too. But they're also often irritable, and they don't always say that they're sad. They might become restless, deliberately injure themselves, get into arguments, abuse alcohol or drugs, or eat or sleep more or less than usual.

Research by Yang and others has begun to sketch a picture of how this affliction takes root in a teenage brain. In some teens, a combination of genetics, childhood trauma, and increased social and academic pressure may cause the brain's emotion circuitry to become hyperactive, magnifying feelings of fear or



HOW TO TRAIN YOUR BRAIN

UCSF scientists are testing an intervention for teen depression called Training for Awareness, Resilience, and Action (TARA) that's based on emerging insights into the teenage brain. The 12-week program consists of four modules, each designed to target different brain areas that may be miswired in depressed teens.

1 CALMING THE MIND
TARA starts with breathing exercises that quiet emotion centers like the **amygdala**, an area associated with fear, anxiety, and aggression.

2 TUNING IN TO THE BODY
Next, teens learn to pay attention to sensations. This calls on areas that govern awareness, including the **insula**, and stops the brain from engaging in rumination.

3 MANAGING EMOTIONS
In the third module, teens practice recognizing, naming, and regulating emotions. This trains the **prefrontal cortex**, which is still developing during adolescence, to exert control over the amygdala and other areas involved in emotion.

4 TAKING ACTION
Finally, TARA teaches goal-setting and value-based action. These skills further improve the function of the prefrontal cortex and strengthen parts of the reward network, including the **striatum**.

chagrin. At the same time, the reward circuitry that helps teens feel motivated and take pleasure in achievement is understimulated. All of this can produce weak or maladaptive links to the managerial prefrontal cortex, making it even harder for a teen to control strong negative thoughts or emotions, strive for goals, and form healthy relationships.

"Depression impacts a teen at the critical stage in their life, when they're developing social skills," Yang says. "If they're not able to do that, it places them at a huge disadvantage. They're at much higher risk for substance-use disorders, for suicide, for failing academically, and later on in life, for losing jobs and getting divorced." People who go through a bout of depression during childhood also tend to have recurring episodes as adults. "They are more likely to suffer from longer, more frequent, and more severe depressive episodes each time," Yang says. "The depression becomes more and more entrenched and more and more difficult to treat."

The good news, though, is that the same malleability, or plasticity, that makes the teenage brain susceptible to mental illness also makes adolescence an "ideal time to intervene," Yang says. The most effective treatments for teen depression – those backed by the most scientific evidence – include the antidepressant medications fluoxetine (Prozac), escitalopram (Lexapro), and sertraline (Zoloft) and cognitive behavioral therapy (CBT), which teaches people to manage their feelings by changing the way they think and behave. These are what clinicians consider first-line treatments.

But they're far from a sure bet. "It depends on the treatment, but on average, we can get about half of our patients half-better," Yang says.

"There's more and more data questioning how helpful antidepressants really are for adolescents," adds UCSF's Lisa Fortuna, MD, MPH, the Carol Cochran Schaffner Professor of Mental Health and chief of psychiatry at Zuckerberg San Francisco General Hospital. "They're probably most helpful in combination with talk therapy for kids with more severe symptoms. For kids with mild symptoms, the role of antidepressants is less clear."

CBT can help with all levels of depression. But given on its own, it seems to work less reliably in teens than in adults, possibly because it focuses on using the prefrontal cortex to

BRAIN MAP CONCEPT CREDIT: EVA HENJE, OLGA TYMOFIYEVA, AND TONY YANG

regulate emotion – something the adolescent brain is still mastering. "It's funny," Fortuna says. "When I would talk to kids about doing cognitive therapy, they would say, 'What the hell? You're asking me to think. I can't do that when I'm in the middle of some horrible stress or argument.'"

Fortuna often sees children dealing with traumas related to poverty, immigration, abuse, and addiction. Almost 20 years ago, she began giving her patients mindfulness exercises, which seemed to help them learn and use cognitive strategies. "Mindfulness can help young people cut through the static that trauma sometimes creates in their minds so that they can see things more clearly and make decisions for their own self-care," Fortuna says. (She later developed these insights into a program called Mindfulness-Based Cognitive Therapy for adolescents with trauma and substance-abuse disorders, or MBCT-Dual.)

Yang had come to a similar conclusion: To be most effective, an intervention for teen depression should take a "bottom-up" approach – calming the overactive limbic system – in addition to tackling the "top-down" faculties of the prefrontal cortex. In 2013, he decided it was time to put this theory to the test.

BRAIN BOOT CAMP

That year, Henje arrived in Yang's lab as a postdoctoral fellow. Early in her career as a psychiatrist, she had worked in an emergency psychiatric ward in Stockholm and become disillusioned with the standard of care there. "Teenagers would come in who were suicidal, and I was expected to put them on all these drugs," Henje, now at Sweden's Umeå University, recalls. "I did, and then a few weeks later, they would come back and were more suicidal and more anxious. It felt unethical to me."

She opened a private practice offering nonpharmacological therapies and founded a yoga institute, where she taught mindfulness and yoga to address stress and depression. Eventually, she grew curious about how these disciplines alter the body and brain and went on to earn a PhD in clinical neuroscience from the Osher Center for Integrative Health at Sweden's renowned Karolinska Institute.

Since 1998, the Bernard Osher Foundation has established seven such centers around the globe; the first one was at UCSF. The Osher Centers treat patients using a combination of conventional medicine and complementary remedies, including herbs, acupuncture, massage, yoga, and meditation. They also educate physicians and the public about these techniques and conduct research on their effects.

For Henje, UCSF's Osher Center was a "mecca for mind-body medicine." In Yang's lab, she combined her mindfulness and psychiatric expertise with his neuroscience to create what would become TARA, and the Osher Center pitched in to fund a pilot study in 26 teens. By 2015, the team had recruited their first volunteers.

The teens met in groups once a week for three months, sitting in a circle on yoga mats. The training consisted of four modules. Each module lasted three weeks and targeted different brain regions, starting with the emotional limbic system and working up to areas governing attention and cognition. (Throughout TARA, participants also got lessons in nutrition, stress, and sleep.)

During the first module, the teens learned yoga-based movements and simple breathing exercises. One exercise, called square breathing, involves holding the breath between inhalations and exhalations. Another, called ocean breathing, uses a constriction of the throat to make a sound like a wave.

It's thought that such slow and deep breathing induces a sense of calm by engaging the parasympathetic nervous system. This network of nerves relaxes the body – steadying the heart rate, unclenching the muscles, and lowering blood pressure – after moments of stress or danger. Henje and Yang hypothesized that the TARA exercises could quiet the amygdala, a limbic structure that triggers the so-called "fight or flight" response and is especially overactive in teens with depression. This, in turn, could promote healthy connections to the anterior cingulate cortex, which routes communication between the limbic and cognitive centers and which seems to be miswired in depressed teens.

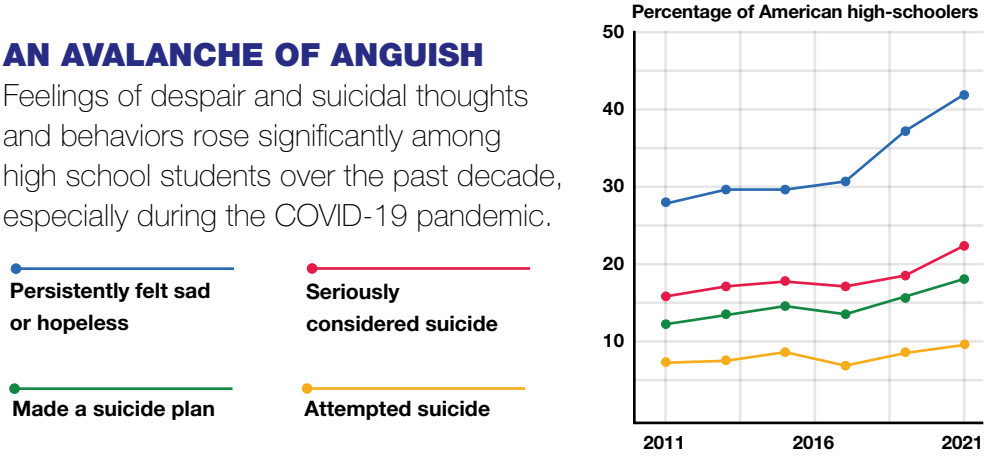
The second TARA module emphasized paying attention to what's going on inside the body. The teens lay down on their mats and slowly scanned their body in their mind's eye, from the top of their head to their toes, noticing what sensations arose. Such exercises call upon the insula – the seat of awareness and interoception, or the ability to perceive one's internal state. Tuning in to the present moment also distracts the mind from worrying: When the insula is preoccupied, the brain has fewer cognitive resources to devote to tasks like negative self-talk and rumination.

In the third module, the teens finally put to work the thinking part of their brain, the prefrontal cortex. They practiced recognizing and naming emotions. They imagined their thoughts and feelings cascading before them, like a waterfall, and watched their anger, anxiety, or boredom tumble down the rapids without themselves being pulled into the turmoil. They discussed how different parts of themselves can think conflicting things – like how one part might wish to die while another part really wants to make the soccer team.

The fourth and last module – meant to strengthen reward structures like the striatum and orbitofrontal cortex – was all about action.

AN AVALANCHE OF ANGUISH

Feelings of despair and suicidal thoughts and behaviors rose significantly among high school students over the past decade, especially during the COVID-19 pandemic.



GRAPH SOURCE: U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION HIGH SCHOOL YOUTH RISK BEHAVIOR SURVEY

The teens shared what they cared about most and created goals that aligned with those values. They dreamed about their future lives and all they would accomplish. Sometimes the discussions veered into existential angst: *If going to school means I'll have a boring job like my parents, what's the point? If the planet is destroyed, what future do I have?*

"These are appropriate questions," Henje says. "Teenagers often feel unheard and dismissed by my generation, which creates a sense of hopelessness or anxiety. I want to validate their experience and say to them, 'There's nothing wrong with you. So much in the world is overwhelming right now, and you are not alone. Coming together with other teens and talking about your feelings and concerns is the first step in creating the future you want.'"

"COMING TOGETHER WITH OTHER TEENS AND TALKING ABOUT YOUR FEELINGS AND CONCERNS IS THE FIRST STEP IN CREATING THE FUTURE YOU WANT."
-EVA HENJE

RAISING RESILIENCE

The pilot study, published in 2017, showed that TARA significantly improved symptoms of depression and anxiety and led to a larger trial funded by the National Institutes of Health that is now underway. Its first phase enrolled 100 healthy teens who, like Lillian, may have had depressive tendencies but no official diagnosis. The main aim was to see how TARA rewired their brains, says Tymofiyeva, an expert in magnetic resonance imaging who is co-leading the new study. (She is also a certified hypnotherapist and an author of young adult fiction.)

Yang and Tymofiyeva launched the trial, called Brain Change, in 2019. But when COVID hit, their team had to adapt TARA for Zoom and restart in 2021. Half the teens took the TARA course online; the other half served as controls. All of the teens' brains were scanned before and after the sessions to compare the outcomes.

"That was the coolest thing I experienced in the study, getting to see my own brain," says Lillian, who was assigned to the TARA group. She particularly liked the breathing exercises and body scans, which she still does sometimes when she's frustrated or anxious. "I'll be in a disagreement with someone or just feel not great, and I'll do square breathing or a body scan for five minutes," she says. "It makes me feel more grounded and able to look at other people's perspectives."

She says she also has become more aware of how her choices, such as what she eats or what songs she listens to, affect her mood. "If I'm feeling down, I'm not going to start playing demeaning music about 'effing bitches' and stuff like that." She still regularly struggles with anxiety, she says, "but I have a lot better coping mechanisms to deal with it."

Lillian also sees a therapist now and has tried other treatment programs, her mom points out, so it's hard to know how much of an impact TARA has had. But she has noticed that Lillian seems to be more motivated to use some of its tools after practicing them with a group of peers.

"Other teenagers were doing it, so it made it a little less uncool," Lillian agrees, although she wishes she could have met her fellow participants offline. "I didn't get to form real connections with them," she says.

Yang and Tymofiyeva are now analyzing the data from the first Brain Change cohort and, according to preliminary reports, have shown that the teens' brains indeed have changed – particularly in areas associated with emotion, awareness, and reward. Encouraged by these findings, the researchers have begun recruiting a new cohort of 120 teens with elevated depression. They expect to see even greater therapeutic benefits and neural rewiring in this group than in the healthy volunteers.

Experts are optimistic that programs like TARA – if proven effective and made widely accessible online or in schools – will help slow or even reverse the steep decline in mental health among adolescents. But early interventions are only part of the solution. There will always be teens who need more specialized mental health care, and many of them will turn to pediatricians, who often are the only providers with availability.

"The need is so big that pediatricians are now regularly seeing really tough cases, and of course they are overwhelmed," says Anne Glowinski, MD, the Robert Porter Distinguished Professor and division chief of child and adolescent psychiatry at UCSF. Most family doctors, she notes, lack the training or resources to manage psychiatric care. "We need to move some of that care to pediatrics to grow our workforce, but it needs to be done thoughtfully and deliberately so that providers feel knowledgeable and supported and not dumped on." (Pediatricians in California can find resources and consult with psychiatrists through UCSF's Child and Adolescent Psychiatry Portal.)

Hospitals will also need to vastly expand their capacity to care for kids who are suicidal or in danger of harming themselves or others. The younger, sicker, and poorer a child is, Glowinski notes, the fewer options they have; families frequently wait hours or even days in emergency rooms for open beds.

In San Francisco, there are zero beds dedicated to mentally ill children and around 18 to adolescents, located at St. Mary's Medical Center. A planned youth psychiatric center at Zuckerberg San Francisco General Hospital will add another 12 beds for adolescents. And at UCSF Benioff Children's Hospital Oakland, which opened an outpatient center for youth mental health services in May, plans for a new hospital building include an inpatient mental health wing with as many as 24 beds for young children and teens.

Coming of age today means facing a future that looks increasingly precarious. As the editors of *The Lancet* recently wrote, a teen of Lillian's age has "gone through the great recession and the subsequent austerity measures, a pandemic with disrupted schooling and social isolation, a cost-of-living crisis, war in Europe, and a world coming to terms with the magnitude of climate change." Our children will confront challenges we never imagined. We can't shield them from adversity, but we can help them build the resilience they need to face it and thrive.

How Gene Therapy **Saved a Child** from 'Bubble Boy' Disease

By Jess Berthold Photo by Barbara Ries

When Hataalii Tiisyatonii "HT" Begay was born on April 7, 2018, his family members rejoiced in the hospital in Tuba City, Arizona, and on the remote Navajo Nation reservation where they lived. Within days, however, the family's exuberance gave way to fear. HT was found to have Artemis-SCID – the most serious form of primary immunodeficiency, also known as "bubble boy" or "bubble baby" disease. Children with Artemis-SCID lack a functioning immune system and are highly susceptible to infections. Most die before their first birthday.

HT was eventually airlifted with his parents to UCSF to meet with pediatricians Mort Cowan, MD, and Jennifer Puck, MD, internationally known experts in SCID. The standard treatment for Artemis-SCID is a bone marrow transplant from a donor, ideally a matched sibling. "Artemis-SCID is one of the hardest genotypes of SCID to treat," notes Cowan. "When you don't have a matched sibling, it has only about a 50% survival rate, even with modern transplant technology."

While at UCSF, the family learned that neither HT's brother nor his parents were a match. But, as luck would have it, Cowan and Puck had just embarked on a clinical trial for a new kind of Artemis-SCID treatment – transplanting a child's own gene-corrected stem cells, rather than a donor's cells. The family chose to participate in the trial, and the procedure, in June 2018, went off without a hitch. HT became the first child in the world with Artemis-SCID to receive gene-correction therapy. "They agreed to be pioneers for this treatment," says Cowan. "They really led the way."

After a long recovery, HT is now back in Arizona living the life of a normal kid. He gets to pet horses, gather eggs, and help tend cattle and sheep – all unimaginable without treatment. His favorite toys are airplanes. "He wants to be a pilot when he grows up; he wants to fly from Arizona to San Francisco," says his grandmother, Laverna Shorty, who cared for HT during much of his journey. "And he says he is going to take his grandma with him everywhere he goes."

The Cancer Breakthrough Boom

Engineered immune cells. Supercharged scans. Drug implants. Gene manipulators. Blood biopsies. A flurry of innovations could change how we confront cancer.

BY ELIZABETH DAUBE ILLUSTRATIONS BY SCOTT BAKAL

Cancer sucks. Chances are you know someone who's had it, or it might have threatened your own life. Too often, a diagnosis demands answers to impossible questions. Which body parts are you willing to live without? Would you risk feeling awful for a while, presuming the treatment might buy you more years of life? Would you settle for one year? How about a few months?

The same cellular feats that can help your skin stitch itself back together are also at work in tumors. The challenge is to kill the cancer cells – which are the patient's cells, just dividing wildly – without also killing the patient. Unfortunately, cancer can be as complex as we are. Worried about, say, one genetic mutation making your cells go rogue? Try many mutations, all helping the cancer thrive at your expense. That's not unusual. And there are hundreds of types. People don't get "cancer" anymore. They get, say, triple-negative breast cancer characterized by the absence of estrogen-receptor, progesterone-receptor, and human-epidermal-growth-factor-receptor-2 expression.

Scientists no longer expect to find a convenient, one-size-fits-all cure. But they *are* finding ways to outsmart this disease. Whether in five years or 50, advances in research underway now could transform how humans cope with cancer.


BAKAL

Implants and Pumps

Keeping Toxic Treatments Where They Belong

The side effects of traditional cancer treatments can be serious. Hair loss. Weight loss, sometimes courtesy of regular vomiting. Loss of red blood cells, also known as anemia, which causes exhaustion. Some treatments for cancer are so toxic that they make *you* toxic; writer Caitlin Flanagan described her first round of chemotherapy as an "absolute hell" that included instructions to avoid hugging her children.

Chemotherapy and radiation work by stopping cancer cells from replicating so rapidly. Unfortunately, some other, rather important cells – like your hair follicles or the lining of your digestive tract or your bone marrow – also divide quickly. That's why researchers are working to corral cancer treatments and the damage they can do.

For example, cancers in the lining of the abdomen can be difficult to treat with typical chemotherapy, which circulates throughout the body. The latest approach, offered by UC San Francisco's Mohamed Adam, MD, goes like this: Surgeons take out obvious tumors, pump chemotherapy right into the abdomen, then drain it back out. The idea is to bring the battle right to the cancer's doorstep but leave surrounding neighborhoods unscathed.

Surgeons are also implanting pumps during operations for cancer that's spread to the liver, offering patients a way to get chemo exactly where they need it – at doses much higher than they'd get with systemic treatment. Ajay Maker, MD, head of UCSF's Division of Surgical Oncology and the Maurice Galante Distinguished Professor, hopes to test newer immunotherapies with pumps, too.

Another potential breakthrough: tiny, silicone-based implants that deliver steady doses of a drug. Clinical trials for the implants are underway for prostate cancer patients at the National Cancer Institute, with plans to develop a similar initiative for breast cancer.

Prostate and breast tumors are often treated with drugs that disrupt sex hormones. These drugs can also prevent breast cancer in women with BRCA mutations, who face an exceptionally high risk of developing the disease. Unfortunately, like other systemic treatments, the drugs don't have an exclusive effect on cancer cells; they impact the whole body. Some men with prostate cancer have told their physicians they'd rather die than take antiandrogens, which are sometimes referred to as "medical castration." And women on estrogen modulators report symptoms of menopause, from hot flashes to depression, that disrupt their lives daily.

Pamela Munster, MD, hopes the implants will dial down the side effects of these drugs. She directs early-phase clinical trials and co-leads the Center for BRCA Research at UCSF's Helen Diller Family Comprehensive Cancer Center, and her lab created the implants. She says they could be relatively simple to put in. Munster compares the concept and materials to the intrauterine device, a contraceptive that women replace about every five years.

"But they're a lot, lot smaller – see how tiny?" Munster says, displaying a scan of the silicone devices embedded in a prostate. Inserted with a biopsy needle, they're just a few millimeters long. Munster envisions a future in which BRCA-positive patients could safely choose the implants over mastectomies, having them removed temporarily if they opt to give birth and breastfeed.

"Whenever I see a patient with a BRCA mutation who is 25, and we talk about planning a risk-reducing mastectomy, that individual will ask me, 'Is there nothing else?'" says Munster, who carries a BRCA2 mutation herself. "Localized drug delivery is so new, and it is very difficult to prove that something can prevent cancer. It takes a long view. It takes precise engineering. But patients need this. My own children might benefit from this one day."

DNA-Driven Solutions

Targeting Tumors' Genetic Fuel

There are many kinds of cancer, but they all have one theme in common: They've broken free of the rules that govern cell growth, repair, and death. Genetic research aims to figure out why the cancer causes so much trouble. Many mutations can drive it, hitting the gas pedal on cellular growth or cutting the brakes that ought to slow it down.

This knowledge has led to new therapies that target specific genetic mutations by throwing a wrench into the cancer's replication machinery. But some mutations have been difficult to disrupt. For many years, researchers considered KRAS, the most common genetic driver of tumors, to be the undruggable "Death Star" of cancer.

The KRAS gene makes a protein that guides cellular growth. "KRAS is normally doing good things in cells," explains Charles Craik, PhD, a professor of pharmaceutical chemistry at UCSF. "But when it mutates, then the brakes are off, and it's a runaway train."

Kevan Shokat, PhD, a UCSF biochemist and Howard Hughes Medical Institute investigator, succeeded where others had given up. He collaborated with Jonathan Ostrem, MD, PhD, a graduate student then and assistant professor of hematology and oncology now, and Ulf Peters, PhD, a postdoctoral fellow at the time. Together, they searched for new ways to manipulate KRAS activity and understand the structure of the protein it makes – ultimately revealing a previously unknown pocket on the surface of mutated KRAS protein to which drugs can bind.

It was a big deal. Shokat received the Sjöberg Prize and the National Academy of Sciences' Award for Scientific Discovery. The research inspired a flurry of drug development, and in 2021, sotorasib became the first therapy approved by the U.S. Food and Drug Administration (FDA) for a cancer caused by KRAS mutations. Craik says this lung cancer drug could become just one of many new regimens tailored to KRAS-fueled tumors.

"The mutant KRAS, the bad actor, is only in the tumor cells," Craik says. "This target is much more specific than just rapidly dividing cells. When you look at how chemotherapies work, you're just poisoning the cancer cells more than you're poisoning the normal cells. Now we have a chance to do true precision medicine."

Exciting, right? Except cancer is tricky. As thrilling as sotorasib's launch was, Craik and Shokat anticipated that some KRAS-driven lung tumors would prove resistant to the drug. It doesn't happen to every patient, but it happens. The cancer adapts, and the treatment stops working. It's called acquired resistance.

"Sure enough, some of those patients got resistance," Craik says. "The tumor was shrinking, but all of a sudden, it starts coming back."

There's also inherent resistance: additional genetic tweaks or chemical pathways that enable a patient's particular cancer to bypass a treatment. Craik adds: "While KRAS is present in lung, colon, and pancreatic cancers, sotorasib currently only works in lung cancer. It doesn't work in colon cancer. It's not that you develop resistance in that case. It doesn't work right from the get-go."

That doesn't mean hope is lost. Researchers are investigating treatments that deliver a one-two punch: first disrupting the mutated KRAS, then disabling the cancer's other resistance tools. Craik and Shokat have developed a new therapy that pulls mutated KRAS to the surface of cells, essentially flagging them as cancer. Then an immunotherapy can help the body remove all the flagged cells. They think this approach might work especially well combined with sotorasib.

"If we can help the immune system spot tumors it wasn't finding before, maybe we can add durability to these targeted drugs," Craik says. He adds that the research is ongoing – not quite ready for a clinical trial, but full of potential: "If we're successful, we're not limited. We could do this with other irreversible inhibitors against other genetic targets. This isn't just a KRAS story."

A Well-Armed Resistance

Reprogramming Immune Cells to Attack Cancer

Theoretically, your immune system *should* hunt down cancer cells and eliminate them before they can turn into tumors. The immune system is kind of like a security team, monitoring the body and removing sources of bad behavior. Your T cells are essential members of this team.

Unfortunately, cancer has clever ways to dodge security. It can secrete molecules or recruit other cells that stop T cells from doing their job, sort of like slipping these immune guards a strong sedative. It can also cloak itself, changing how it expresses antigens. Cells usually display antigens on their surface like an identity card, and the T cells check whether they belong in your body or need to get booted out. By changing how they express antigens, cancer cells basically become invisible – free to slip past the T-cell bouncers and cause some *Road House*-level mayhem.

Immunotherapies treat cancer by overcoming these defenses. A relatively new approach, chimeric antigen receptor T-cell (CAR T) therapy, has quickly become one of the most promising tools in the treatment arsenal.

"The T cells can be pretty much blind to the tumor," explains Justin Eyquem, PhD, an assistant professor of microbiology and immunology. "One way to make the T cells see the tumor again is to add a new gene to the T cells."

In CAR T, scientists take some of a patient's T cells and genetically engineer them, training the T cells to recognize a different antigen on the cancer and latch onto it. Then the medical team injects the revamped T cells back into the patient, where they can track down the cancer cells much more easily than before. So far, CAR T works well for certain types of blood cancers, like leukemia.

"These leukemia patients had already tried all the other treatments available," Eyquem says. "Remarkably, about 50% to 90% of them get what we call a complete response from the CAR T. That means a few weeks after one injection of these T cells, you cannot detect the cancer in their body anymore. That is a paradigm shift."

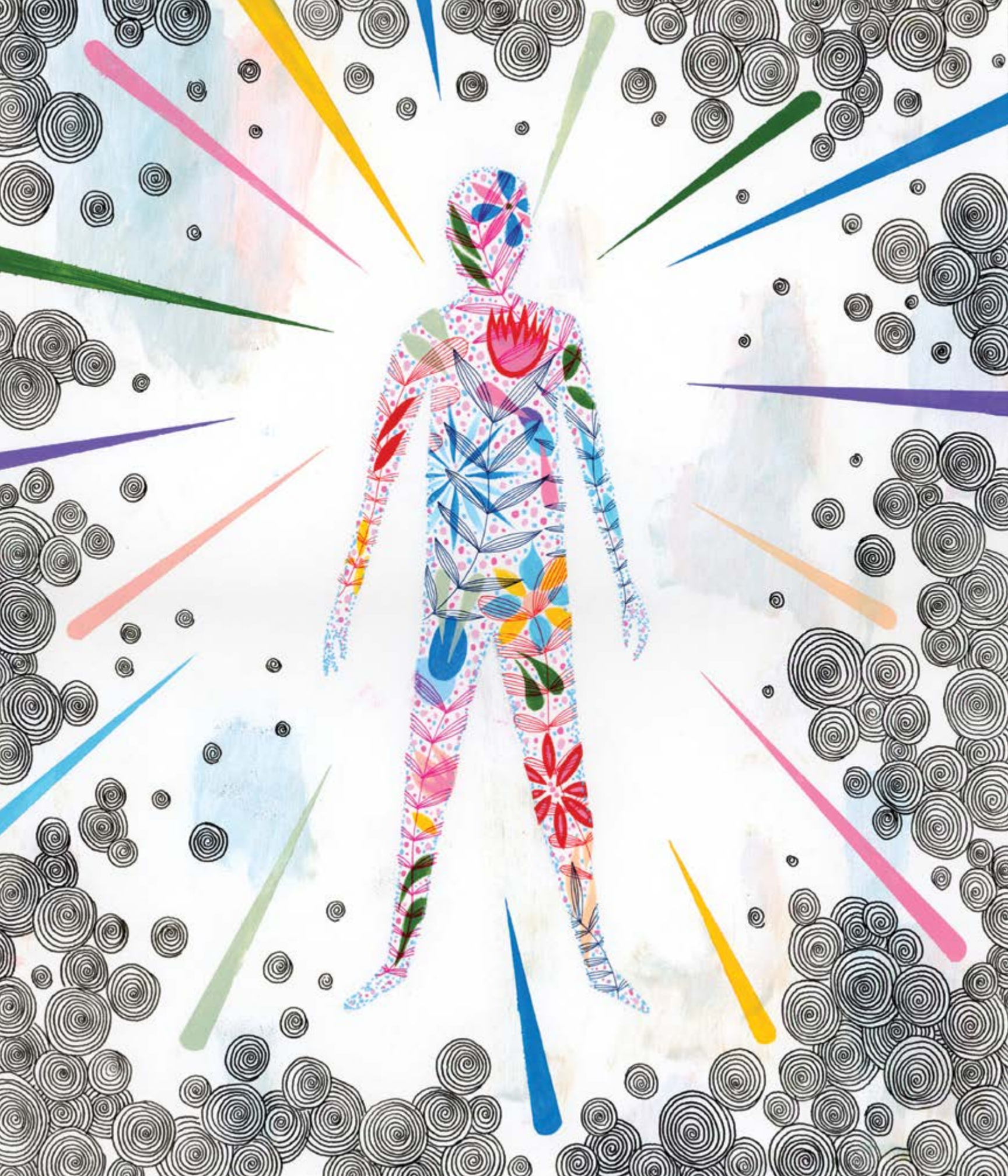
The CAR T targets an antigen that's expressed exclusively by the leukemia and by B cells, a kind of white blood cell. You can't live long with zero B cells because your body needs them to make antibodies, which fight off infection. But people receiving CAR T can survive by getting infusions of antibodies instead.

It's not all amazing news, though. For some patients receiving CAR T, the cancer eventually returns. Perhaps the patient's cancer evolves, cloaking its antigens even better than before. Maybe the modified CAR T cells just don't persist long enough to attack all the cancer. Plus, blood cancers aren't quite like solid cancers. The latter involve tumors, which have more immune defenses – including dense networks of blood vessels that feed and protect them.

Eyquem and other researchers are working to improve CAR T, making it more effective and expanding its reach beyond blood cancers. For example, his team has invented a new, ultrasensitive type of receptor that could supercharge T cells, helping them spot even the lowest levels of cancer antigens. Another UCSF team, led by Julia Carnevale, MD, an assistant professor of hematology and oncology, recently used CRISPR technology to identify genes that can boost engineered T cells. So far, in mice with tumors, these tweaked T cells last longer and work more effectively than non-boosted T cells.

Meanwhile, other UCSF scientists have created combination receptors for CAR T, which require several antigens to activate the T cells. You know how two-factor authentication makes you log in and enter a code from your phone to confirm it's you? Combination receptors work kind of like that. They could be useful for cancers with antigens that are also expressed in healthy organs. You want the T cells trained to attack the cancer – only the cancer, not your perfectly serviceable brain cells.

To accelerate its production of CAR T cells, UCSF recently started manufacturing them at a new facility run by Thermo Fisher Scientific. Researchers are also trying to find affordable ways to scale up treatments like CAR T. Right now, it's extremely expensive to produce made-to-order T cells for each patient.



"One day, we could move from cell therapy to gene therapy," Eyquem says. "The idea is not to take your T cells out and engineer them but instead inject the vector that is going to engineer the cells directly into the patient. It's still a bit science fiction, but it's exciting."

High-Tech Blood Tests

Catching Cancer When It's Easier to Eliminate

Lacking cures for late-stage cancers, some researchers have focused on helping people get diagnosed long before their tumors turn deadly. Early-detection tools for some tumors already exist: colonoscopies, mammograms, blood tests for a worrisome prostate biomarker. But many kinds of cancer have no such test. By the time they're discovered, the damage is already done.

"For the deadliest, most common form of ovarian cancer, we're still diagnosing at stage 3 and 4 about 90% of the time," says Jocelyn Chapman, MD, the Berson Family Professor of Gynecologic Cancer. "I'd like to detect ovarian cancer when it's at stage 0, when we can do surgery and that's the end of that."

Chapman and her colleagues are trying to create a blood test for ovarian cancer. They're part of a new frontier in early detection, as biotech companies race to develop "liquid biopsies" that could curb cancer deaths.

Scientists have known for a while that cancer cells release genetic material. The trick to an ideal blood test lies in figuring out which parts of that material reliably predict cancer.

To solve this problem, Chapman is collaborating with Nadav Ahituv, PhD, director of UCSF's Institute for Human Genetics. His research focuses on neomers, short segments of DNA that are altered in cancer but not in normal tissue.

"Neomers are scattered all over the genome, which makes them a bit more useful than just looking at one or two gene mutations," Chapman says. "It's not like we can look for a single strand of DNA that changes in one way and then go, 'Aha! That's ovarian cancer.' Instead, we're looking for a specific kind of pattern. When you see that pattern over and over again, it's like a cancer fingerprint."

If researchers like Chapman and Ahituv succeed, we might one day look back on the era when cancer spread silently in the body and call it archaic – not unlike the time before fire alarms, when people were usually choking on smoke before anyone had a clue the house was burning.

"At the beginning of my career, I thought all I was going to do was operate on people, give them chemotherapy, and watch them die a few years later," Chapman says. "I would have given those patients some time. But the technology has dramatically improved. I'm hopeful that this will actually change before I retire. Maybe we can give people not just a few years, but many, many years."

Nowhere to Hide

Lighting Up Cancer Wherever It Lives

For many years, the best way to tell if a tumor had metastasized was by using anatomic imaging: scans that combine a series of X-ray images into a rough picture of your insides.

But anatomic imaging is not a precise way to track down all your cancer cells. Thomas Hope, MD, a professor of radiology, led a clinical trial that helped UCSF and UCLA gain FDA approval to provide the first PSMA PET scans for U.S. prostate cancer patients. Since then, the new imaging technique has taken off. Today, patients across the country are getting the scans.

PSMA stands for prostate-specific membrane antigen, a protein found on most prostate cancer cells. The new technique uses positron emission tomography (PET) plus a drug that binds to PSMA, illuminating prostate cancer cells anywhere they reside in the body.

"Before PSMA PET, we didn't know where the disease was," Hope says. "In essence, PSMA PET shines a light on it."

Once doctors know exactly where the cancer is, they can get to work removing it. Peter Carroll, MD, MPH, UCSF's Derr-Chevron Distinguished Professor of Prostate Cancer and Taube Family Distinguished Professor of Urology, and Hao Nguyen, MD, PhD, the Grinold Professor of Urology, are bringing PSMA-targeted imaging into the operating room. Participants in their clinical trial get a compound that attaches to PSMA. Then surgeons use a camera that highlights those cells, helping them remove traces of cancer that might have been impossible to spot otherwise, even with the latest robotic surgical tools.

"The cure rate for patients with high-risk prostate cancer has not changed over the last 20 years," Nguyen says. "About 30% still get a recurrence after surgery. We want to find all the invisible bits of cancer and remove them completely because that could save lives and reduce the need for additional treatment."

Meanwhile, Hope is collaborating with researchers like Vadim Koshkin, MD, an assistant professor of hematology and oncology, to investigate ways of using PSMA-targeted technology to treat advanced cancers that can't be eliminated with surgery alone. The treatments work like a key that only fits a PSMA-specific lock, delivering damage to cancer cells and skipping healthy ones. They just launched a trial for prostate cancer patients using radiation therapy that binds to PSMA, plus a drug that increases PSMA expression. In theory, the combination could outperform existing treatments, possibly with fewer side effects.

The improved imaging made possible by PSMA PET will inspire much more research that aims to customize cancer treatments, Hope says. "Before, we gave systemic therapy because we didn't know that, for example, a patient had disease in only one lymph node. Now that we know exactly where the cancer is, maybe we get to do something different – something better."

You'll Soon Be Able to Get a Blood Test for Alzheimer's

Will you want one?

By Adam Piore Illustrations by Giulio Bonasera

When Daniel Gibbs, MD, enrolled in an Alzheimer's study at UC San Francisco almost a decade ago, researchers needed access to a secure government facility just to confirm that he had the disease. They summoned Gibbs to the Lawrence Berkeley National Laboratory, hooked him up to an IV, and wheeled him into a donut-shaped machine called a PET (positron emission tomography) scanner. Then they waited.

In a building next door, radiochemists fired up a cyclotron, a huge contraption equipped with powerful magnets. The magnets spun tiny particles faster and faster, ultimately creating a nuclear reaction that produced radioactive molecules known as tracers. The tracers were designed to safely detect markers of Alzheimer's in the brain. But soon after they were created, the molecules would begin to decay. So they had to be transported to Gibbs immediately.

The radiochemists placed the time-sensitive cargo in a plastic cylinder the size of a large soda bottle and sent it hurtling through a network of pneumatic tubes. The cylinder arrived in Gibbs' room with a loud "woosh" and a "thud." The UCSF researchers quickly extracted the tracers and transferred them into his IV tube. "It was timed down to the second," recalls Gibbs, a retired neurologist who, ironically, had spent his career caring for patients with Alzheimer's. "They had stopwatches running."

The tracers traveled through Gibbs' bloodstream into his brain, where they latched onto abnormal proteins that

are characteristic of Alzheimer's disease. Only then, using the PET scanner, could the researchers peer inside the black box of his brain. On the scans, clusters of the tracers lit up like constellations.

At the time, the test Gibbs received was cutting edge – and heralded by many in the field as a tantalizing glimpse of the future of Alzheimer's diagnostics. For decades, the only way for a family to know for sure if their loved one had the disease was by having their brain autopsied after they died. PET scans allowed physicians to bring certainty to patients during their lives.

But even today, few people suspected of having Alzheimer's ever receive such testing. Although longer-lasting and more convenient tracers exist today, PET scans still come with financial and logistical hurdles. Neither Medicare nor Medicaid will pay for Alzheimer's scans, which cost upward of $5,000 a pop. And patients often must travel to major cities to get them. (Biomarkers of Alzheimer's can also be detected in spinal fluid – a less expensive test but one that requires a lumbar puncture, which is uncomfortable and invasive, so many patients choose not to get one.)

"The diagnosis gave me some certainty about what I was dealing with." – DANIEL GIBBS

Scientists may have finally found a way to overcome these limitations. In 2020, researchers at UCSF and elsewhere unveiled several groundbreaking studies of a new, highly sensitive blood test developed in the labs of the pharmaceutical company Eli Lilly. The studies demonstrated that the test could detect tiny concentrations of Alzheimer's-associated proteins in patients' blood with remarkable accuracy, even before the onset of cognitive symptoms. Since then, other research groups have announced additional promising blood tests for the disease. Experts say the U.S. Food and Drug Administration (FDA) could approve the first of these tests by the end of the year.

Blood tests are less expensive than PET, less invasive than a lumbar puncture, and easy to use, which means they likely will become far more widely used than the other diagnostic options. The early versions now go for around $1,200 to $1,500, about a quarter the price of a PET scan, and the cost should fall as the market expands. Many experts are optimistic that a boom in accessible Alzheimer's tests could enable new insights into the disease, speed the development of new treatments, and radically improve patient care. More patients could learn – as Gibbs did – that their brains harbor signs of Alzheimer's disease as early as 20 years before cognitive troubles start.

But these advances also raise vexing questions. What does it mean if you test positive for Alzheimer's biomarkers but have no symptoms? How certain is it that you will develop the disease? Should you try new medications that could slow its progression but might also cause serious side effects? Would you want to know that you could one day face a devastating illness for which there is currently no cure?

WORTH A THOUSAND WORDS

In 1901, a 51-year-old woman named Auguste Deter walked into a German asylum with a variety of strange symptoms, including memory loss, paranoid delusions, agitation, problems with sleep, and mental confusion. "I've lost myself," she remarked before she died four years later, according to the records of her doctor, Alois Alzheimer, MD.

After Deter's death, Alzheimer autopsied her brain. He noticed that the thin outer layer, or cortex, was shrunken. And when he examined slices of it under a microscope, he saw dark clumps of sticky "plaques" and stringy "tangles" in and among the nerve cells. These plaques and tangles would come to be recognized as the hallmarks of Alzheimer's disease.

But the problem of how to spot them in living patients stymied the field for almost a century. Without definitive diagnostic tests, the elderly were condemned to maddening uncertainty: Were flashes of forgetfulness or confusion just "senior moments" or signs of impending precipitous decline?

Even patients clearly suffering from dementia were often misdiagnosed. Clinicians had trouble distinguishing between Alzheimer's and other brain disorders with similar cognitive symptoms, such as frontotemporal dementia and atypical parkinsonism. This made it difficult for doctors to adequately advise families and likely confounded the results of many early drug trials. (Between 1998 and 2017, pharmaceutical companies made 146 unsuccessful attempts to develop Alzheimer's medicines.)

In the early 1980s, scientists identified the key proteins comprising plaques and tangles: amyloid beta and tau, respectively. By the next decade, they had shown that these compounds were detectable in spinal fluid using a lumbar puncture, also known as a spinal tap. And in 2004, radioactive tracers like those used on Gibbs, which made it possible to see Alzheimer's proteins on a PET scan, made their debut.

Gil Rabinovici, MD, who began a fellowship in memory disorders at UCSF's Memory and Aging Center a year later, recalls how exciting it was to observe the brain "at a molecular level" in order to diagnose a disease that, according to

what he'd learned in medical school, could only be revealed after death. The Memory and Aging Center, which was then emerging as a national leader in research and care of Alzheimer's disease and other causes of dementia, was one of the first places in the country to adopt PET technologies. In the clinic, Rabinovici saw how valuable these tests could be for patients.

"They say a picture is worth a thousand words," he says. "As much as patients respected our expert opinions, seeing the scan results with their own eyes really made all the difference in the world. It ended their quest for a diagnosis and allowed them to move toward thinking about next steps."

That was certainly true for Gibbs. Before undergoing the PET scan, he had taken a genetic test and learned he was carrying two copies of a gene that placed him at extremely high risk of developing Alzheimer's disease. Suddenly, every misplaced key, forgotten name, or other mental stumble began to take on dark undertones. He found the ambiguity maddening. But then, at age 63, he found himself staring at his own brain on a conference room screen. The tissue, rendered in black and white, was shot through with clusters of red and yellow, highlighting areas where the radioactive tracers had found and bound to amyloid plaques.

Receiving a clear-cut answer was a life-changing relief. "The diagnosis gave me some certainty about what I was dealing with and going to have to deal with more in the future," says Gibbs, who detailed his experience in a 2021 book, *A Tattoo on my Brain: A Neurologist's Personal Battle against Alzheimer's Disease*. "It allowed me to focus on the disease and how I could lower the impact of it and plan for the rest of my life."

In 2016, Rabinovici, who now specializes in PET imaging and is UCSF's Fein and Landrith Distinguished Professor of Memory and Aging, helped launch a massive study of PET tests called Imaging Dementia: Evidence for Amyloid Scanning (IDEAS). Still ongoing, the study aims to enroll 25,000 Medicare beneficiaries with mild cognitive impairment or dementia at hundreds of clinical sites across the country to determine whether amyloid PET scans improve patient care and outcomes. The results to date, Rabinovici says, are unequivocal: The scans have had a "profound impact on diagnosis and patient management."

In an analysis of 11,000 IDEAS participants published in 2019, Rabinovici's team found that about a third of patients who got PET scans had previously received *wrong* diagnoses; after the tests, clinicians switched their diagnosis from Alzheimer's disease to a non-Alzheimer's cause, or vice versa. For more than 60% of patients, the tests also led to changes in care, such as new drug prescriptions or counseling. Unpublished data from IDEAS has even demonstrated a modest impact on medical outcomes, including a 4.5% reduction in hospitalizations, Rabinovici says.

The study is now in a second phase called New IDEAS, which focuses on reaching populations, such as Black and Latinx communities, that have been historically underrepresented in Alzheimer's research. Initial data suggest that patients from these groups are less likely than white patients to test positive for amyloid plaques on PET scans. This implies that for such patients, conditions other than Alzheimer's, such as cerebrovascular diseases, may play a larger role in the development of dementia.

"In dementia care, we've been diagnosing people based on symptoms of memory loss or other cognitive changes," Rabinovici says. "But if we're going to make progress in treatment and prevention, we need to understand the biological underpinnings that are driving their symptoms."

BLOODWORK BREAKTHROUGHS

For early adopters like Rabinovici, the advent of PET scans underscored the importance of biomarker testing for Alzheimer's disease. But experts were unable to solve the technology's accessibility problem.

Blood tests have always been an obvious answer. Scientists long suspected that modified forms of amyloid beta and tau could be found circulating in the blood of Alzheimer's patients. A handful of studies published between 2007 and 2014 showed it might be possible to detect these proteins in blood samples, but the studies could not be replicated. Until recently, blood tests simply were not sensitive enough to measure the tiny concentrations of blood proteins with sufficient accuracy and consistency.

In the late 2010s, researchers at Eli Lilly created the first breakthrough product. Its innovation was a proprietary antibody – a large, Y-shaped protein that attaches to a form of tau called P-tau217, making the tau molecules easier to see and measure. The test immediately caught the attention of Adam Boxer, MD, PhD, a UCSF neurologist and the Endowed Professor of Memory and Aging.

Boxer directs clinical trials for Alzheimer's disease and frontotemporal degeneration at the Memory and Aging Center. When he heard about Eli Lilly's test, he was studying a rare neurodegenerative disorder called progressive supranuclear palsy (PSP), which is often misdiagnosed as Parkinson's disease. Searching for better diagnostic tools, Boxer had become fascinated by a strange phenomenon: Like Alzheimer's, PSP is marked by a toxic proliferation of tau in the brain, but researchers could find surprisingly little tau in the spinal fluid of PSP patients. Maybe, Boxer thought, the tau proteins were leaking into their blood instead.

Elisabeth Thijssen, PhD, then a doctoral fellow in his lab, set out to explore this hypothesis using Eli Lilly's powerful new test. Initially, the results were disappointing. Thijssen could find no more tau in the blood of PSP patients

than in the blood of people with other conditions, including Alzheimer's. But when she and Boxer looked more closely at the data, they noticed there was far more tau in the blood of the Alzheimer's patients than in any other group's blood. If they could replicate this finding in a larger study, it would be big news.

Tapping into Boxer's clinical research network, Thijssen and her collaborators tested the blood of hundreds of patients with Alzheimer's disease and frontotemporal degeneration, one of the diseases most commonly misdiagnosed as Alzheimer's. They were pleased to find that blood concentrations of tau were 3.5 times higher in the Alzheimer's patients than in the other participants in the trial. Although half of the patients with frontotemporal degeneration also had tau in their brains, the Eli Lilly test could distinguish between the two populations with 96% of the accuracy of an autopsy.

Thijssen, who now works in consulting in her native Netherlands, presented the results at the Alzheimer's Association International Conference in July 2019 (and later published them in *Nature Medicine*). At the same conference, two other research groups reported similar observations. One study, in people with a genetic mutation that causes early-onset Alzheimer's, showed that the blood test was just as capable as a spinal tap or PET scan at detecting early biological signs of the disease, which can emerge 20 years before cognitive symptoms do. The studies generated worldwide headlines and inspired the development of other promising blood tests.

Researchers still need to better understand the potential limitations of the new tests, Boxer says. It's possible, for instance, that medications or co-existing medical conditions affect their performance. But he expects that those final hurdles will soon be cleared and that blood tests could start being offered in clinics later this year. The biggest beneficiaries, he predicts, will be "people who have trouble accessing health care," including underserved populations in the United States and abroad.

AN EMERGING DEBATE

As they await the FDA's approval of the new blood tests, experts have begun to debate how they should be used – and what exactly the results mean. For instance: When does a positive test indicate that a patient has or will develop Alzheimer's disease?

Ken Covinsky, MD '88, MPH, a UCSF geriatrician who often works with Alzheimer's patients and their families, notes that many people die with amyloid plaques in their brains but never develop dementia during their lifetimes. What if blood tests had revealed those plaques years before their deaths? Would that have caused them to worry unnecessarily or pursue harmful treatments they didn't need?

Blood tests can measure tau tangles as well as amyloid plaques, and there is more evidence directly linking tangles

to the onset of cognitive deficits. Still, warns Covinsky, UCSF's Edmund G. Brown Sr. Distinguished Professor of Geriatrics, "we should proceed with extreme caution." The widespread availability of biomarker tests, he concedes, will enable earlier diagnoses. "But what exactly are you diagnosing? It's hard to know what to make of these biomarkers without knowing who is truly going to get dementia."

Maria Glymour, ScD, a UCSF epidemiologist, says the key question when rolling out a new diagnostic tool should always be: Is this going to improve life for patients? "Fundamentally, what people care about is memory loss and cognitive impairment," she says. "If you define a disease based on a biomarker, with no incorporation of patient perspectives, you can 'cure' the disease by removing the biomarker without improving anything that the patient experiences."

These concerns are particularly salient now that new, controversial drugs designed to remove amyloid plaques are entering the market. So far, the FDA has approved two drugs in this class, aducanumab and lecanemab, through its accelerated approval program. While the drugs seem to modestly slow cognitive decline, neither comes close to curing the disease. Both also are expensive – now close to $30,000 a year – and can cause brain bleeds and other side effects whose long-term impacts have not yet been studied. Prescribing these drugs

based solely on biomarker tests might not be in patients' best interests, Covinsky cautions.

But others argue that for patients who wish to try all options, an early, biology-based diagnosis could allow them to benefit while their brains are still relatively healthy. Lecanemab, the more effective of the two drugs, can preserve the ability of some Alzheimer's patients to function on their own for as much as a year and a half longer, Rabinovici says. The drugs' side effects, he adds, are rarely severe and almost always resolve when patients stop taking the medications.

"If you wait to initiate treatment until people develop full-blown dementia, treatments like lecanemab won't work," Boxer notes. "Many patients come into our clinic at a stage that is too advanced for them to benefit." Blood tests, he maintains, could change that. "There is now strong evidence that some blood tests are very accurate predictors of who will develop symptoms of dementia over the next three to five years," Boxer says. He points to a large clinical trial called AHEAD that is using the tests to help identify people with Alzheimer's biomarkers before they show cognitive symptoms and assess whether lecanemab can delay memory loss. The trial, funded by the National Institutes of Health and Eisai Inc., a developer of the drug, is currently enrolling participants at UCSF and other sites across the U.S. and Canada.

And drugs aren't the only option for patients who test positive for Alzheimer's biomarkers. Lifestyle changes can make a big difference in outcomes, says neuropsychiatrist Kristine Yaffe, MD, director of UCSF's Center for Population Brain Health and one of the world's leading experts on cognitive decline and dementia. Yaffe, the Scola Professor of Psychiatry and Epstein Professor of Geriatric Pyschiatry, studies what she calls "modifiable risk factors." Her research has shown, for instance, that getting sufficient high-quality sleep dramatically decreases the risk of developing Alzheimer's disease. Healthy habits like staying physically active and eating a plant-based or Mediterranean diet are also protective, Yaffe says, because they help control other conditions that affect cognition, including hypertension, diabetes, obesity, and high cholesterol.

Recently, Yaffe led a two-year trial in a large group of healthy elderly volunteers to evaluate the effectiveness of prevention strategies. Each participant had at least two identifiable risk factors associated with cognitive decline, such as poor sleep, exercise, or diet. Half of the participants worked with a health coach to improve those factors; the other half served as controls and received only educational materials. The study demonstrated that the intervention worked. At the end of the trial, participants in the experimental group reduced their risk factors to a greater extent and performed 80% better on cognitive tests than those in the control group.

Daniel Gibbs, who was unaware of any family history of Alzheimer's before his own tests, says his diagnosis inspired his whole family to take proactive measures.

"There is now strong evidence that some blood tests are very accurate predictors of who will develop symptoms of dementia over the next three to five years." – ADAM BOXER

Because he has two copies of his Alzheimer's risk gene, his children all inherited at least one copy. "They know they're at risk," he says, "and they're cognizant of the things they need to do to reduce that risk going forward."

THE SURGEON SET ON CURING GENETIC DISEASES BEFORE BIRTH

UCSF's Tippi MacKenzie is leading groundbreaking clinical trials of therapies aimed at stopping fetuses from developing devastating disorders.

By Kirsten Weir

PHOTO: NOAH BERGER

Five-year-old Elianna loves running around with her big brother in their yard on the Hawaiian island of Kauai. She isn't afraid to get dirty, is learning to ride a bike, and has her doting grandfather wrapped around her little finger. It's a delightfully ordinary childhood – but one that almost didn't exist.

When Elianna's mom, Nichelle Obar, was pregnant with her, an ultrasound revealed that her tiny heart was enlarged and fluid surrounded her lungs. Follow-up testing confirmed a shattering diagnosis: alpha thalassemia major. The inherited disorder disrupts the production of hemoglobin, the protein in red blood cells that's responsible for delivering oxygen throughout the body. Without treatment, most fetuses with the condition die before birth.

"I was devastated, thinking that my child would not survive," Obar recalls. "But whether it was perfect timing or divine intervention, our genetic counselor happened to be attending a webinar that week with Dr. MacKenzie."

Tippi MacKenzie, MD, a pediatric and fetal surgeon, directs the UCSF Center for Maternal-Fetal Precision Medicine and the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research. In 2017, when Obar first heard about her, MacKenzie was just beginning a clinical trial to evaluate a pioneering way of treating alpha thalassemia in the womb. Experts have known for decades that in utero blood transfusions, delivered through a vein in the umbilical cord, can save a sick fetus's life. But children born with the condition still need treatment throughout their lives, and the procedure isn't offered everywhere; many expectant women never even learn it's an option until it's too late.

"Have there been any human trials?" Obar asked. "No," MacKenzie replied. "You'd be the first."

MacKenzie's trial was offering transfusions, along with something new: a stem cell transplant that could potentially cure the disease. After getting in touch with the UC San Francisco team, Obar and her husband, Chris Constantino, pored over the trial details. They learned that doctors would insert a needle into the center of Obar's hip bone to collect her bone marrow, the spongy tissue that produces stem cells. The doctors would then process the marrow to extract these immature cells and inject them into her umbilical vein. If all went according to plan, Obar's stem cells would move into her fetus's bone marrow, where they would mature into blood cells – including the healthy red cells the baby needed.

The couple also learned that the trial was based on extensive research that MacKenzie and her colleagues had done in animals. "The first thing I asked was, 'Have there been any human trials?'" Obar recalls.

"No," MacKenzie replied. "You'd be the first."

The response gave Obar pause. But MacKenzie, the John G. Bowes Distinguished Professor and a Benioff UCSF Professor, doesn't shy away from firsts. More than four decades ago, her role model, Michael Harrison, MD, performed the world's first successful fetal surgery at UCSF. MacKenzie is now continuing that legacy, looking beyond performing operations in the womb to delivering medical procedures that treat genetic diseases before a child is born. She envisions a future where fetal therapy is routine for correcting inherited disorders, including rare diseases like Elianna's and more familiar ones like cystic fibrosis and sickle cell disease.

When MacKenzie talks about her research, her dark eyes light up behind her round glasses. But when asked to describe what makes her successful, her gaze falters. She has no interest in claiming center stage. "This isn't my work," she stresses. "There's an enormous team of people that makes this possible."

Her colleagues, on the other hand, have no trouble shining the spotlight on her. "Tippi is a brilliant scientist, and her work is truly cutting-edge," says her collaborator Juan Gonzalez-Velez, MD, PhD. A UCSF maternal-fetal medicine specialist, he performed the in utero blood transfusion and stem cell transplant for Elianna and has continued to do so for subsequent babies in MacKenzie's studies. "It opens up a whole new avenue for prenatal treatments, which could be expanded to so many other disorders."

FETAL SURGERY IS BORN

In 1981, after testing fetal surgery in pregnant sheep, Harrison was granted institutional approval to operate on a human fetus. The first, historic procedure – to reroute a blocked urinary tract – saved a boy's life. Harrison went on to found the UCSF Fetal Treatment Center at Benioff Children's Hospitals, where he and his colleagues set the bar for operating on the tiniest, most fragile patients. During one of those cases, as Harrison carefully sliced a tumor from an unborn baby, an eager medical student named Tippi watched from the corner of the OR, transfixed.

Born Tippi Cicek, she spent her early childhood in Istanbul, Turkey, before her family moved to the U.S. when she was 11. She was a voracious learner: "Reading, math, science – I loved all of it," she says. Also a talented classical pianist, she studied at the Julliard School of Music. But fate had another plan for her capable hands.

After college at Harvard, where she majored in biochemistry, she moved west for medical school at Stanford. There, she heard a surgical resident utter the phrase "fetal surgery," which stopped her in her tracks.

Born at UCSF Medical Center, Elianna was the first baby to receive an in utero stem cell transplant to treat a lethal form of thalassemia. Now 5 years old, she is thriving at her home in Hawaii.

PHOTO: WALTER ZARNOWITZ

"Oh, my God, people *do* that?" she asked him. When she learned that Harrison had pioneered the field, she picked up the phone and arranged to do a month-long rotation at UCSF. "Watching Dr. Harrison resect a tumor from a fetus was the most extraordinary thing," she says. "I remember being in that room and thinking, 'This is what I want to do.'"

Around the same time, in 1996, she read an article in the *New England Journal of Medicine* describing the first in utero stem cell transplant. Alan Flake, MD, a pediatric and fetal surgeon at Children's Hospital of Philadelphia (CHOP), and his colleagues had performed the procedure on a fetus with severe combined immunodeficiency (SCID). Children with SCID are born with virtually no immune system. Defenseless to infection, few survive their first year. By transplanting stem cells taken from the bone marrow of the child's father, Flake's team appeared to have found a cure.

That paper stayed in the back of MacKenzie's mind as she continued her training. During her surgical residency at Harvard's Brigham and Women's Hospital, she reached out to Flake to ask about research opportunities. "It was before email, so I sent him a fax," she laughs. That led to a three-year fellowship studying stem cell transplantation and gene therapy with Flake at CHOP, where she also received additional training in pediatric and fetal surgery.

Her time in Flake's lab started MacKenzie on a line of research she's continued to this day. But as she and others in the field would soon discover, fetal stem cell treatments turned out to be much more complicated than that first test case had suggested.

OF MICE AND MOTHERS

After Flake's success curing a fetus of SCID, researchers tried transplanting stem cells into unborn babies with a variety of blood and other immune disorders. "Most of the time, it just didn't work," MacKenzie says. "And that was a bit of a mystery."

But the fact that it had worked for SCID – a disease that wipes out the immune system – offered an important clue. The human immune system is built to be wary, attacking anything it identifies as foreign. Before a child or adult undergoes a stem cell transplant, they must take powerful drugs to prevent their immune system from waging war on the donor cells. When MacKenzie began her research, most experts believed that the fetal immune system was immature and therefore wouldn't reject stem cells from a donor. But SCID aside, that's exactly what seemed to be happening.

Finally, in 2008, UCSF infectious disease specialist Mike McCune, MD, PhD, now retired from the University, made a surprising discovery. During pregnancy, some of the mother's cells pass into her developing child through the placenta. The fetus exists in harmony with these cells, McCune showed, by manufactuing special immune cells whose job is to dial down its own immune response. "That's part of why pregnancies can be successful even though mother and child are not genetically identical," MacKenzie says. "We've always intuitively understood it's important that the mom doesn't reject the fetus, but it's just as important for the fetus to not reject the mom."

For years, most physicians attempting fetal stem cell transplants had taken the cells from someone other than the mother. "Nobody wanted to harvest cells from a pregnant woman," MacKenzie says. "But if we know the fetus doesn't reject Mom," she wondered at the time, "why aren't we using maternal cells?" This, she suspected, could be a more reliable approach.

She tested the theory in her lab, and it was soon clear she was on the right path. Transplants in fetal mice were more successful with maternal cells than with nonmaternal ones, which were destroyed soon after being transplanted. But MacKenzie also found some-

MacKenzie confers with her lab manager, Maria Clarke. Her team is exploring new tools for treating fetal diseases, such as gene therapy and RNA-based drugs. "There's a lot coming down the pike," she says.

thing else remarkable: The immune cells of the fetal mice weren't the only ones killing off the nonmaternal cells. The mother's immune cells, wandering freely inside the fetus, also swooped in to join the assault – another reason to transplant maternal cells.

Those experiments were the basis for the clinical trial that ended up saving Elianna's life. Obar was about halfway through her pregnancy when she learned about MacKenzie's study, and her unborn baby was growing sicker by the day. She and Constantino packed their bags and flew to California.

Elianna was the first of six fetuses treated in the UCSF trial. All the babies were born at full term and are doing well, according to MacKenzie, who continues to monitor their progress. The study was a phase I trial, so its main goal was to assess whether in utero stem cell transplants are safe; the team is now evaluating their effectiveness.

Fetal therapy may have given these children a chance at life, but it's not yet the cure that MacKenzie is aiming for. Five years later, Elianna still needs blood transfusions every month or so. Not enough of Obar's cells survived in her daughter to heal her completely.

In retrospect, MacKenzie says, alpha thalassemia may have been a tricky test case to start with. The decision had been a practical one. Some physicians, like Gonzalez-Velez, were already treating the condition with fetal blood transfusions, so adding stem cells into the mix would likely pose little additional safety risk. But, as is often true in medical science, the biology of the disease turned out to be thornier than MacKenzie had anticipated.

Because alpha thalassemia deprives a fetus of oxygen, the unborn baby's bone marrow seems to churn out extra red blood cells in an attempt to overcome the deficit. The proliferation of native red cells might prevent donor cells from establishing themselves, MacKenzie reasons. "These fetuses are so sick, and their own bone marrow is so revved up, that it may be hard for the maternal cells to survive," she says.

Even so, her trial has helped raise awareness that alpha thalassemia is no longer a hopeless diagnosis. Despite the availability of fetal blood transfusions, many doctors still believe the disease is too severe to treat, MacKenzie says. For reasons that baffle her, some pregnant women are never even told treatment is an option, and their fetuses die in the womb. "It's heartbreaking how these patients have been ignored by the medical community, even though with blood transfusions they can survive to birth and live as normal kids," she says. "The most rewarding thing has been shining a light on this condition."

MacKenzie is now preparing the trial results for publication, and she's hopeful they will lay the groundwork to move ahead with trials of fetal stem cell treatments for other inherited diseases. She's eyeing other forms of thalassemia, as well as Fanconi anemia, a rare and life-threatening disorder that affects all types of blood cells. "Even if these diseases are rare individually, they add up to a lot of conditions that we could treat before birth," she says.

INTO THE UNKNOWN

One thing that's certain about focusing on fetal therapy: You have to be willing to venture into the unknown. Harrison waded in when he made the case for operating on a fetus with no other options. Years later, he recognized the same quality in MacKenzie and helped recruit her to UCSF. "I always thought Tippi had tremendous potential," he says. "Something about her said she'd take on the hard challenges. She just does it, and she doesn't blink."

Only three years after meeting Elianna's family, MacKenzie launched another groundbreaking clinical trial. This one would be the first in the world to test fetal therapy for a group of inherited metabolic disorders called lysosomal storage diseases (LSDs). People with LSDs don't make enzymes that break down waste in cells. As a result, toxins build up in their tissues, causing symptoms that can include organ damage, skeletal abnormalities, muscle weakness, intellectual disabilities, and developmental delays. The effects are debilitating and often fatal.

Synthetic enzyme therapies are available for a handful of LSDs. Given regularly through intravenous infusions, these treatments can slow a disease's progression. But even when therapy is started shortly after birth, irreversible damage may already have been done. MacKenzie had shown it was safe to inject stem cells into fetuses. Why not do the same with enzymes?

Once again, she took the question into the lab. As she had hoped, fetal enzyme therapy helped prevent organ damage in mice with LSDs. And there was another benefit to the early intervention. Many LSDs cause neurological problems, and most enzyme therapies given after birth can't cross into the brain. During pregnancy, however, a fetus's blood-brain barrier hasn't yet formed. MacKenzie showed that enzymes

PHOTO: MAURICE RAMIREZ

given to mice in utero could migrate to their brain cells and clear out any toxic buildup there.

Based on those results, the U.S. Food and Drug Administration approved MacKenzie's human trial in 2020. Getting permission from the FDA to test a fetal therapy is an enormous challenge – even more so in this case because MacKenzie's team wanted to test the therapy not just in one disease but in the eight LSDs for which enzyme therapies are available. "Tippi is probably the most effective person I've ever worked with," says Paul Harmatz, MD, a UCSF gastroenterologist who specializes in LSDs and is collaborating with her on the project. "I'm still amazed we were able to get this trial approved."

MacKenzie's unwavering determination may be the reason a Canadian toddler is alive today. The child's parents had lost two daughters to an LSD known as severe infantile Pompe disease when they learned their unborn baby had inherited the same metabolic disorder. This time, though, there was reason for hope.

But just as the trial was scheduled to begin, the COVID-19 pandemic threw a curveball into the team's plans. With borders locked down, the Canadian family couldn't travel to California. Undeterred, MacKenzie shared the details of her treatment protocol with the family's Canadian medical team and helped them gain regulatory approval to give the therapy off-label, outside the UCSF trial. That baby is now a toddler who babbles and walks and smiles – milestones that few babies with severe infantile Pompe disease ever reach.

A LEAP OF FAITH

Since the Canadian case, MacKenzie and her colleagues have treated two patients with LSDs as part of the UCSF trial, and they plan to enroll eight more. Even if they prove that fetal enzyme therapy can slow disease progression and prevent organ damage, it won't be a cure. After the children are born, they will continue to need regular enzyme replacements.

But it's an exciting time for LSD treatment, Harmatz says. Several promising therapies that can cross the blood-brain barrier are now in clinical trials or likely to be approved soon. And with new treatments poised to improve long-term outcomes for many children with LSDs, fetal therapies may one day play an even bigger role in preventing serious symptoms before birth. "This can be a bridge to a cure," Harmatz says. "It's a huge step forward."

Some of the next advances may come from MacKenzie's lab. "There's a lot coming down the pike," she says. Among the many lines of research she's exploring is gene therapy, which involves editing or replacing gene variants that cause diseases like alpha thalassemia. She's also testing fetal infusions of RNA-based drugs in mice. These drugs could potentially treat inherited neurological diseases by switching genes on and off or blocking the production of harmful proteins. And she continues to study how maternal and fetal cells coexist – and whether a breakdown in the immune cease-fire may play a role in kickstarting preterm labor.

It's a lot to juggle, especially for a mom of two busy teenage daughters. To fit it all in, she made the hard decision in 2021 to set down her scalpel and give up operating. "Being a surgeon is central to my identity," she says, though it was never her singular focus. Her patients have always been her North Star.

> "Even if these diseases are rare individually, they add up to a lot of conditions that we could treat before birth."
>
> –Tippi MacKenzie

Because the fetuses in her clinical trials have genetic conditions, many of the families she cares for have already lost one or more pregnancies or have other children or relatives who are affected. MacKenzie's work requires hard conversations – and decisions that are harder still. Her job, she says, is to help families decide what's right for them, whether that's trying an experimental fetal therapy, waiting until after birth to begin treatment, or terminating the pregnancy. "The central tenet of fetal therapy," she emphasizes, "is to present all the options and let the pregnant woman choose."

After all, MacKenzie says, she's not the star of this story. "To have that leap of faith…" she says. "I think of my patients as the heroes."

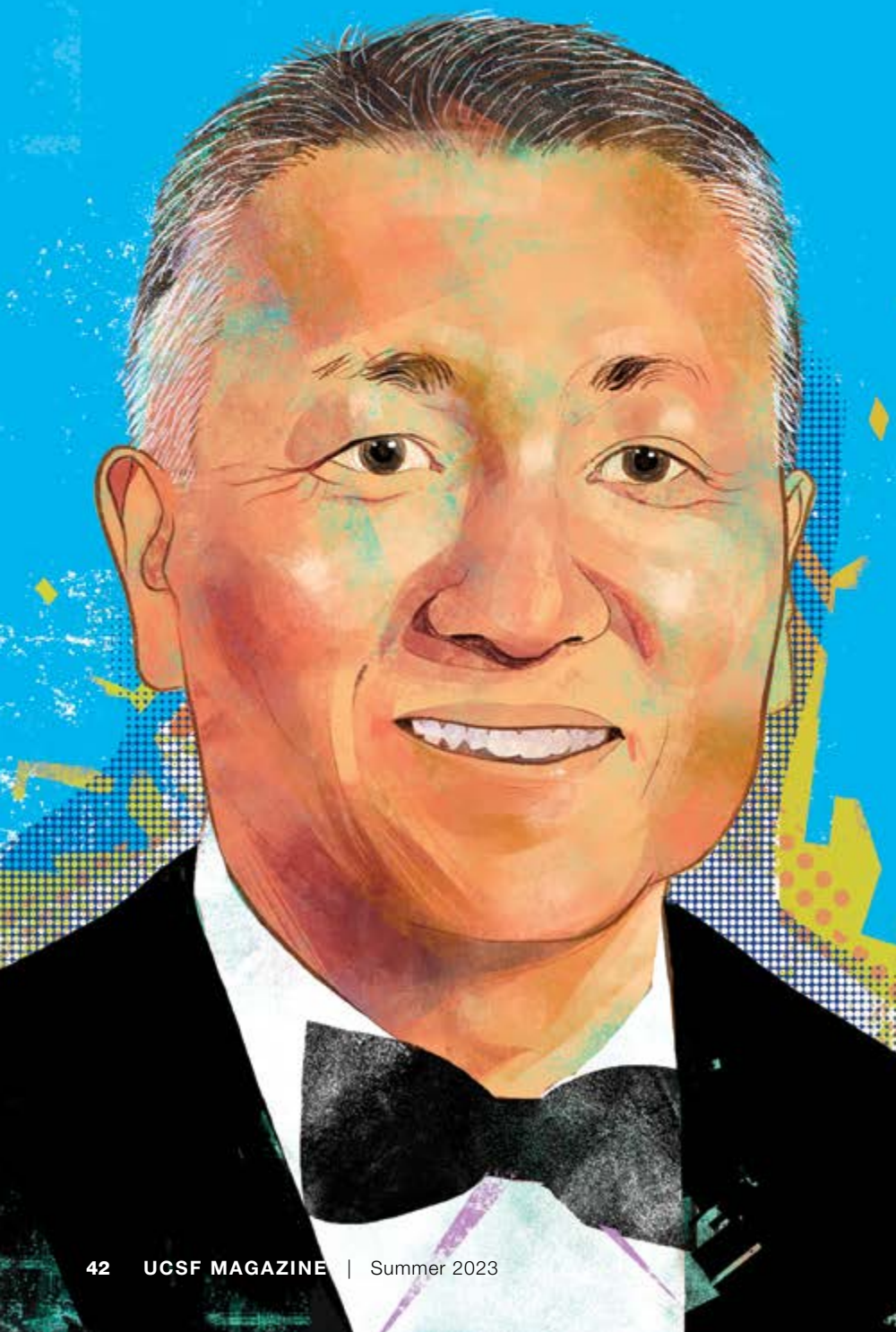
MacKenzie holds newborn Elianna with her mother, Nichelle Obar.

PHOTO: BARBARA RIES

ALUMNI HUB

Meet UCSF's 2023 alumni of the year, selected by their alumni associations for their outstanding contributions to health and humanity. Read their full profiles at **alumni.ucsf.edu/stories**.

By Dora Dalton Illustrations by John Jay Cabuay



SCHOOL OF DENTISTRY

Ted Wong, DDS '84, MHA, MSS

Serving the Nation as a Dental Leader

AWARD

Medal of Honor

AN OFFICER AND A DENTIST

During his exceptional 30-year military career, Wong became the first officer in the U.S. Army Dental Corps to lead two regional medical commands and two major medical centers, overseeing tens of thousands of patients as well as medical and dental residents. He eventually attained the rank of major general and was the first Chinese American selected as chief of the entire Army Dental Corps.

FAMILY FOOTSTEPS

Wong is the son of Po-Ping Wong, DDS '65, who received the same UCSF Medal of Honor in 2013. "He was probably my biggest cheerleader and biggest motivator," Wong says of his father. "He was there for all of the ups and downs."

TREASURED TIMES

"I got to care for what I consider the most deserving people in the nation – America's sons and daughters, those that have volunteered to defend our way of life at the risk of their own."

GRADUATE DIVISION

Carol Camlin, PhD, MPH, Postdoc Alum

Striving to End the HIV Epidemic in Africa

AWARD
Alumna of the Year

UPENDING AIDS
In the early 1990s, HIV's dire impact on Camlin's friends and community propelled her to pursue AIDS education and activism. It eventually led her to Kenya to work with the communities where the epidemic began. Now a UCSF professor, social demographer, and behavioral scientist, she studies how human mobility contributes to the spread of HIV in Southern and Eastern Africa and develops interventions for the many people still in the epidemic's grip.

INTELLECTUAL SPARK
Camlin's protégés describe her as an exceptional mentor who is committed to fostering the next generation of HIV prevention researchers. "I take great pleasure in seeing my trainees and mentees succeed," she says. "And it's intellectually interesting to me to think about the processes through which people learn and grow and develop."

LIFE ADVICE
"I say to my mentees, 'You don't really have to have a grand life plan. You only really have to know what you want to do *next*. As long as you're true to your values and your passions, it all just sort of unfolds naturally.'"

SCHOOL OF DENTISTRY

LaJuan Hall, DDS '94

Helping Patients and the Profession Shine

AWARD
Medal of Honor

DENTISTRY DYNAMO
Hall has run a busy pediatric dentistry practice in the Bay Area's East Bay for almost 25 years, while also finding time to serve in leadership positions in the California Dental Association and the American College of Dentists, train UCSF students as a volunteer faculty member, and contribute her energy and expertise to numerous UCSF boards and committees. Hall exemplifies "excellence, ethics, professionalism, and leadership in dentistry," wrote a colleague who nominated her for the award.

BEYOND THE CHAIR
Hall considers her real success to be going beyond the dental needs of her patients and their families and serving their hearts and minds long after they were children in her chair. She offers career guidance, helps with college applications, and more. "That's been probably the main driver for me as a dentist – not so much the actual work of dentistry but the influence you have on children as a pediatric dentist," she says.

DEEP REWARDS
"I've been really blessed. Every day when I go to work, I have the opportunity to make a difference in a child's life – and not just with their smile."

SCHOOL OF PHARMACY

Sheila West, PharmD ’71, PhD

Improving Eye Health Around the World

AWARD

Alumna of the Year

EYES ON PUBLIC HEALTH

A trailblazer in public health whose work takes her to Asia and Europe and all over Africa, West is vice chair for research at the Wilmer Eye Institute and the El-Maghraby Professor of Preventive Ophthalmology at Johns Hopkins University. Early on, she became involved with a career-defining study, the two-decade Salisbury Eye Evaluation project, which looked at the effects of sunlight and other factors on the eyesight of a multiethnic population in Maryland. Her subsequent investigations have deepened the profession’s understanding of eye diseases and of ways to improve eye health globally.

FUTURE VISION

West found her path while working in the Philippines, where a colleague – an ophthalmologist who studied eye diseases – convinced her that the field was ripe for exploration. “I don’t even like eyes,” she remembers thinking. But she saw a future in them. “It was a time when very little was happening with public health in ophthalmology. It’s exciting when you can come into a field and be a pioneer.”

’60S INFLUENCE

“Coming into San Francisco in 1967 and living three blocks north of Haight-Ashbury, I think it’s safe to say we probably were the most out-there pharmacy class. My fellow students and the political atmosphere at the time shaped me in a way that made my career path clear.”

SCHOOL OF NURSING

Naomi Schapiro, MS ’96, PhD ’12, PNP

Advocating for Underserved Young People

AWARD

Jane Norbeck Distinguished Service Award

A CHAMPION FOR IMMIGRANT YOUTHS

Schapiro “totally fell in love with working with teenagers” during a nursing stint at juvenile hall in San Francisco. After earning her MS from UCSF, Schapiro began working with teenage immigrants from El Salvador, Guatemala, and Mexico in Bay Area clinics. Also driven by a strong sense of social justice, she went on to devote much of her career as a professor in the UCSF School of Nursing to improving the health and lives of immigrant youths.

TRAGEDY SPAWNS CAREER PATH

A car accident when Schapiro was a teenager left her with serious injuries and her sister a paraplegic. Her sister had to rehabilitate far from home, and their parents, also severely injured, were emotionally unavailable. “People didn’t give us very much information about what was going on,” she says. “It was really the nurses who helped me and my sister through what had happened.”

PROTÉGÉ PRAISE

“Naomi’s deep devotion to improving care for the underserved, and her incredible persuasiveness in enlisting mentees to address clinical or educational gaps, always propel me to think outside of my own comfort zone and to join her in these efforts,” wrote one nominator.

SCHOOL OF MEDICINE

Pamela Sutton, MD '73

Helping Terminally Ill Patients Live Well

AWARD

Alumna of the Year

AHEAD OF HER TIME

Sutton started practicing palliative medicine 20 years before it became a recognized specialty. A pillar in the field for decades in South Florida, she rose to the position of director of palliative care services for the North Broward Hospital District, where she has trained 10 palliative medicine fellows who have gone on to influence the field themselves. She has also journeyed to Pakistan, India, and Ethiopia to offer care and training, working privately and with the World Health Organization.

INSPIRED BY SERVICE

As an adolescent, Sutton read about the humanitarian work of two notable physicians – French-German Nobel laureate Albert Schweitzer in Africa in the early 1900s and American Thomas Dooley in Southeast Asia in the 1950s. She felt moved by their service and says their examples were what pointed her toward palliative care. Later, at her UCSF graduation, she was honored with the Gold-Headed Cane, an award that recognizes extraordinary "spirit of service."

IN THE END

"I have no illusions that I'm going to save my patients, but if I can give them some comfort, if they can have good quality time with their family and some perspective and some peace, then I did something. That's how I look at it."

Sliding Down

By Michael Rabow, MD

Bodega Bay
April 6, 2021

Every parent knows the question,
A suggestion, really,
Asked and offered with nothing but love –
No challenge to independence
Or skill or bravery.

Do you want to
Slide down on your butt?
Just the hard part
Just the steepest part
With the eroded soil
And the rotted wooden planks.

Here was my beautiful wife
Asking me
A grown man
Her man
With whom she'll stick,
No matter what,
Even after the MS progresses further
And I cannot even slide anymore.

Bristling a little with the question,
I wondered privately
How *will* I get down?
And do I really deserve
such a sweet woman
Caring if I do?

Michael Rabow, MD '93, is the Helen Diller Family Professor of Palliative Care at UCSF. *Sliding Down* won first place in the 2021 Paul Kalanithi Writing Contest.

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PHOTO: STEVE BABULJAK

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