

UCSF

MAGAZINE

Winter 2019



Stopping violence in our communities

Mending the physical wounds
is only the beginning

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Exploring why some of us seem immune to the ravages of time

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A WAY OUT OF PAIN

Jamal, a gunshot victim, learned to paint on his path toward a new life. Read his story on page 31.

COVER ILLUSTRATION: EDELY RODRIGUEZ. THIS SPREAD: GABRIELA HASBUN

At UCSF, we know our success is inextricably tied to the strength of the communities that surround us.

Despite sustained economic growth and wealth, our region is still struggling with serious and systemic problems that call for all of us to take bold action. We cannot and should not ignore the humanitarian crises happening on our streets – whether homelessness, substance abuse and mental illness, or the daily violence that plagues our most underserved communities.

We are pursuing many opportunities to reaffirm our commitment and increase our contributions to the community, such as leveraging UCSF's expertise to help address the mental health and substance abuse issues that are detrimental to so many who live on the streets. Our cover story, for example, focuses on the Wraparound Project at Zuckerberg San Francisco General Hospital and Trauma Center. The Wraparound team works tirelessly to stop the cycle of adversity that traps many victims of gun violence. It is just one of a great many UCSF efforts to solve health inequities in our communities.

Elsewhere in this issue, we explore the disturbing fact that the prevalence of sugar in our food supply is making some of us *very* sick – and delve more deeply into why it is extremely difficult for our society to overcome the problem.

We also look at a condition no one can escape: aging. Scientists have long studied what goes wrong



as we age. “But in recent years,” writer Adam Piore tells us, “a growing number of researchers ... have turned their attention to a separate ... [question]: What is it that allows some older people to thrive?”

Finally, I invite you to dive into the newest findings on gene editing. Headlines about CRISPR have been hard to miss in recent months – but clear explanations of how this truly revolutionary technology works and what it means for patients have been few and far between. In “The First Genome Surgeons,” writer Ariel Bleicher makes sense of it, while also explaining the central role of UCSF's next generation of specialists who are creating the future of genetic therapy.

Sam Hawgood, MBBS
Chancellor, UC San Francisco
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Settling in for a late night in the lab, Seemay Chou, PhD (below, right), an assistant professor of biochemistry and biophysics, confers with a colleague. Chou's research seeks to uncover the molecular forces that drive the transmission of Lyme disease and other animal-microbe interactions.





A Pioneering Marijuana-Derived Drug for Epilepsy

For the first time, the U.S. Food and Drug Administration (FDA) has approved a drug derived from marijuana – and it may soon offer relief to children with hard-to-treat seizures.

In 2013, a patient at UCSF Benioff Children’s Hospital San Francisco was the first child ever to receive the drug. The results from that initial trial prompted UCSF researchers to expand their study and seek FDA approval.

The drug, Epidiolex, is a purified, liquid form of cannabidiol, a component of marijuana that has anticonvulsant effects without the accompanying “high” produced by one of marijuana’s other components, THC (tetrahydrocannabinol).

“Everybody knew that this could be a good medication for seizures,” says Maria Roberta Cilio, MD, PhD, former director of research at UC San Francisco’s Pediatric Epilepsy Center of

Excellence. But, she adds, “nobody tried.”

Until, that is, Cilio led a 12-week study that tested Epidiolex in 162 patients with severe, childhood-onset, treatment-resistant epilepsy at 11 centers across the nation. Results showed that the medication reduced the frequency of participants’ seizures.

Now, Epidiolex is an FDA-approved treatment for Dravet syndrome, a severe genetic disorder that causes prolonged and often intractable seizures. It is also approved for patients with Lennox-Gastaut syndrome, who experience daily seizures that are difficult to control with standard medications and therapies.

FACULTY IN THE MEDIA

“We need better brains to manage the deluge of information we consume on the internet, on social media, on our smartphones today – as well as the new technologies we’ll surely encounter tomorrow.”

^ Neuroscientist **Adam Gazzaley, MD, PhD**, on the “cognition crisis” plaguing humanity in the information age, in *Medium*

“We know ‘two heads are better than one.’ We’ll soon learn, though, that ‘two heads’ are more complicated as well.”

^ **Gurpreet Dhaliwal, MD**, a professor of medicine at UCSF, on the legal, ethical, and psychological issues involved in using artificial intelligence to aid in diagnosing illness, in the *Wall Street Journal* blogs

“Right now we have a flawed set of metrics.... We place a priority on being first author in a prestigious journal.... Remember, the goal is not to become famous, it’s to discover new knowledge.”

^ **Keith Yamamoto, PhD**, UCSF vice chancellor for science policy and strategy, on the need to make graduate science education more student-centric, in *Science*



Edward Chang is a member of the UCSF Weill Institute for Neurosciences.

How the Brain Controls the “Music of Speech”

Understanding vocal pitch could give realistic synthetic voices to those unable to speak.

We humans are the only primates who can precisely control the pitch of our voices. Fluctuating pitch not only allows us to sing, it also conveys critical information during speech – including mood, emphasis, and even grammar (such as whether a sentence is a statement or a question). In fact, this unique ability likely drove the evolution of spoken language.

Now, new research reveals the brain region responsible for this capability. The study – led by Benjamin Dichter, PhD, formerly a postdoctoral researcher in the laboratory of senior author Edward Chang, MD '04, a professor of neurological surgery – involved monitoring the brain activity of volunteers as they repeated a sentence. By having the volunteers emphasize different words in the sentence, the researchers could see how their brain activity changed with changes in pitch.

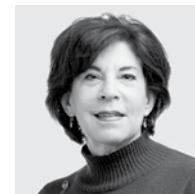
The results showed that activity in one brain area, called the dorsal laryngeal motor cortex, correlated with quick changes in pitch. Neurons in a nearby area were activated when speakers changed their overall pitch, as people sometimes do when they talk to pets or children.

The group’s next project is already underway – exploring whether it’s possible to reverse engineer pitch control: Can they predict which word is being emphasized just by looking at a speaker’s neural activity?

Such insights could pave the way for more naturalistic prosthetic voices for people who can’t speak. “You’d really like a prosthetic to carry the emotional content of the speaker,” Dichter says. “It’s not enough to just capture the words, because so much of what we communicate is *how* we say something.”

PHOTO: BARBARA REIS

How to Support a Friend Facing a Medical Crisis



Cynthia Perlis is director of the Ernest H. Rosenbaum, MD, Art for Recovery program in the UCSF Helen Diller Family Comprehensive Cancer Center. Learn more about her book *Bedside Manners* at bit.ly/ucsf-perlis.

Cynthia Perlis, author of *Bedside Manners: What to Say and What Not to Say When Someone is Ill*, shares her top learnings from 30 years of listening to cancer patients at UC San Francisco.

By Susan Godstone



Show up ... and keep showing up

A complaint Perlis hears a lot from patients is that friends are there for them 100 percent in the first few weeks after their diagnosis, but then they disappear. “If you don’t know what to say, don’t just disappear,” she says. “Sometimes sitting quietly and being there is everything.” Indeed, Perlis contends that showing up is one of the most helpful things you can do for a loved one. She recalls a patient calling it a “beautiful moment” when a friend came unexpectedly, with a favorite book, to visit her at the infusion center.



Help with the simple things

One of the better ways you can help is by taking on some of the person’s mundane chores like cleaning out the fridge, doing the laundry, cooking a meal, or taking the dog for a walk. Asking people what they need is a good start, but sometimes they will have no sense of what they need. In that case, just being present and displaying compassion for what they are going through may be enough. What they really need may then become more evident.



Listen mindfully

There is not a right thing to say but more a right way to be, Perlis says. She recommends mindful listening to better understand who someone is and what they are feeling. Everyone is different and responds to words in a different way. It’s crucial to recognize this, stay in the present for as long as possible, and not rush in with advice. Our natural inclination is to want to make the person feel better, fix things, and offer solutions. But Perlis believes it is not the responsibility of the family member or friend to say “You’ll be all right.” Instead, she suggests, “we need to learn to accept people’s feelings in the moment. There is a real process involved in being able to mindfully listen to someone and hold their feelings without judgment and opinion.”



Show warmth, not pity

“Look people in the eye and show warmth, not pity,” Perlis advises. “Hugging and touching also work.” Most of us in this situation mean well, but being kind and mindfully thoughtful requires putting aside our own fears, feelings, and opinions.

What's Lurking in Your Body?

Scientists can now analyze people's blood for hundreds of harmful chemicals at once.

Each year, tens of thousands of chemicals are manufactured in or imported into the United States, yet experts know very little about which chemicals may enter people's bodies or how these substances may affect human health.

Now, UCSF scientists can screen people's blood for potentially harmful chemicals. They have accelerated a new application of a technique known as high-resolution mass spectrometry. The process identifies chemicals by their molecular weight and makes it possible to screen for many more chemicals at once than previous methods.

In a recent UCSF study that used the technique to screen for approximately 700 chemicals, an average of 56 suspect chemicals per subject were found in blood samples from pregnant women in San Francisco.

The new method specifically screens for environmental organic acids, which are widely used in pesticides and consumer products. People are exposed to these and similar chemicals by using such products, eating contaminated food, drinking



Tracey Woodruff, professor of obstetrics, gynecology, and reproductive sciences



contaminated water, or breathing contaminated air or dust. The substances can cause endocrine disruption, which makes them particularly dangerous to pregnant women and their fetuses, since the chemicals may interfere with fetal development. Plans are already underway to expand the number of chemicals the process can screen for to about 3,000.

“As we suspected, more chemicals are present in pregnant women than previously identified, some of which may be hazardous to the developing fetus and to adults,” says Tracey Woodruff, PhD '91, MPH, senior author of the study and director of UCSF's Program on Reproductive Health and the Environment. “This new process helps us prioritize chemicals for further study and prevention.”

To Improve Patient Care, Design Electronic Health Records for Nurses Too

Today's electronic health records (EHRs) may hinder nurses' ability to do their best work, according to ongoing research by Kirsten Wisner (center), a PhD student at the UCSF School of Nursing and a nursing director at Salinas Valley Memorial Healthcare System. Her findings could lead to improvements in the design of EHR systems.

As these systems become ubiquitous, many clinicians worry that they may impede care as much as they help. Efforts to improve EHRs have focused mostly on relieving physician burden, such as by designing simpler user interfaces and more manageable entry requirements. Nurses' needs, however, have been largely overlooked – despite their daily use of these records to make clinical decisions.



That's a problem, Wisner says. In a pilot study of labor and delivery nurses' perceptions of EHRs, she found that the nurses' biggest concerns included issues with navigating a patient's EHR, with gaining a quick grasp of the patient's overall status, and with interfacing with fetal monitoring systems – all of which made retrieving and synthesizing information more difficult.

Wisner's dissertation research will look more closely at the effect of EHRs on the cognitive aspects of labor and delivery nurses' work, including perceptual, emotional, and intuitive skills. “My hope is that this research will help us better understand the impact that EHRs are having on nurses' work so that we can provide improved tools for nurses and better outcomes for patients,” she says.



Twisting Fate: My Journey with BRCA – from Breast Cancer Doctor to Patient and Back

UCSF oncologist **Pamela Munster, MD**, has advised thousands of women on how to deal with the life-altering diagnosis of breast cancer. But when she got a call saying that her own mammogram showed irregularities, she found herself experiencing a whole new side of the disease. Munster's book weaves together her personal story with her team's research on the BRCA gene, which is responsible for breast cancer and many other inherited cancers.

Read: bit.ly/ucsf-read1-w19



UCSF Osher Mini Medical School for the Public

Learn what goes on every day in UCSF's classrooms and labs from the same faculty who are on the front lines, teaching students in the health professions. These courses for the rest of us delve into everything from the science of sleep to the biological basis of back pain to the latest studies on brain plasticity. Attend in person or watch past lectures online.

Watch: bit.ly/ucsf-watch-w19



***Carry the One Radio* podcast: "Jazz Bands and MRI Scans: How Brains are Creative"**

Have you ever wondered what's going on in a musician's head while they improvise? In this episode, Charles Limb, MD, a UCSF surgeon and neuroscientist, explores the process of creativity by scanning the brains of jazz musicians and rappers as they improvise. Tune in to learn what brain processes allow creative thought and why creativity matters.

Listen: bit.ly/ucsf-listen-w19

Baby Born after First Trial of Fetal Stem-Cell Therapy

Before Elianna was even born, she was a medical pioneer. At four months' gestation, she was diagnosed with alpha thalassemia, a blood disorder that can cause anemia and heart failure. A month later, she was enrolled in the world's first clinical trial to test the safety of stem-cell transplantation in utero – which could eventually be used for prebirth treatment of disorders like beta thalassemia and sickle cell disease.

Tippi MacKenzie, MD, a pediatric and fetal surgeon at UCSF Benioff Children's Hospital San Francisco, led the team that performed the pathbreaking transplant. They delivered immature cells, or stem cells, from Elianna's mother's bone marrow to her fetus. The hope was that the transplanted stem cells would take root in the fetus's own marrow, where they would generate healthy blood cells to alleviate the symptoms.

In January, MacKenzie was delighted to welcome baby Elianna into the world. "We are encouraged by how well she and her mother have tolerated this complex treatment," she says.


 Watch MacKenzie (right) explain her procedure at bit.ly/ucsf-stemtrial



PHOTO: NOAH BERGER

UCSF scientists developed a “biosensor” that reports where and when opioids bind to a matching receptor. When morphine was applied to a nerve cell membrane (in purple in the top panel), the drug rapidly crossed the membrane and within 20 seconds had bound to receptors in an internal cell structure called the Golgi apparatus (bright yellow and white in the bottom panel).

Why You Don't Get Addicted to Your Brain's Own Opioids

Scientists have long assumed that opioid drugs like morphine affect the brain in the same way as do innate opioids like endorphins from exercise or laughter. But this presents a conundrum: Why don't the brain's own opioids cause addiction?

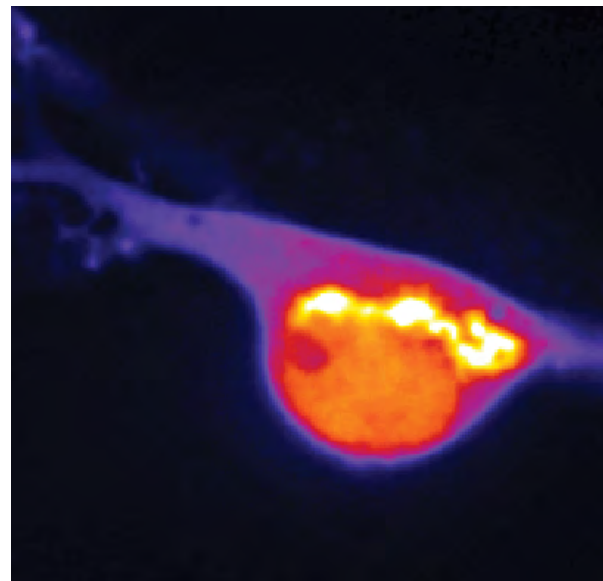
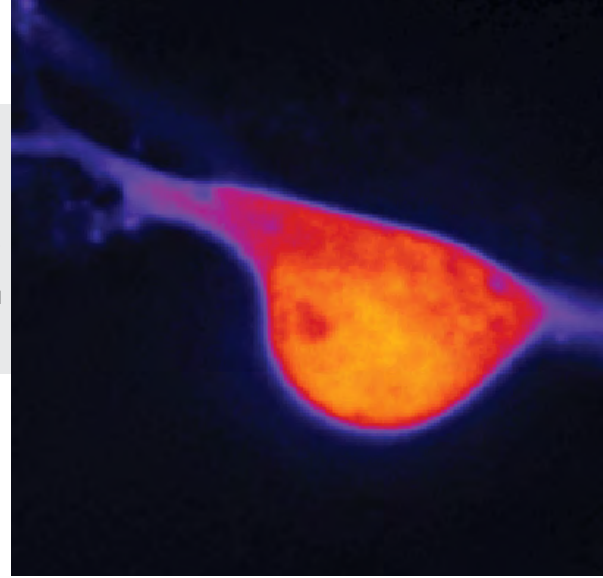
“There has been no evidence so far that opioid drugs do anything other than what natural opioids do,” says Mark von Zastrow, MD, PhD, a member of the UCSF Weill Institute for Neurosciences and UCSF's Friends of LPPI Professor. “So it's been hard to reconcile the experiences that drug users describe – that opioid drugs are more intensely pleasurable than any naturally rewarding experience.”

A new study by researchers in von Zastrow's lab – in collaboration with Aashish Manglik, MD, PhD, an assistant professor of pharmaceutical

chemistry – provides one of the first insights into the puzzle, showing that the behavior of externally and internally made opioids differ in subtle but important ways.

To study these differences, the team created a biosensor to peer inside cerebral neurons, or individual brain cells, giving them a closer look than ever before at opioids' effects. They found that opioid drugs and natural opioids activate receptors inside neurons at different locations and at different rates. “Drugs actually produce different effects by activating receptors in a place that natural molecules cannot access,” says Miriam Stoeber, PhD, a postdoctoral researcher in von Zastrow's lab.

She and her colleagues hope to now apply their findings to create new types of opioid-based pain medications with lower risks of addiction.



E-Cigarettes Raise Risk of Heart Attacks

People who smoke e-cigarettes daily are twice as likely to suffer a heart attack as nonsmokers, according to a new study led by UCSF researchers. When combined with daily use of conventional cigarettes, the risk rises fivefold.

“The finding ... is particularly troubling, because most people who use e-cigarettes continue to smoke cigarettes,” says senior author Stanton Glantz, PhD, director of the UCSF Center for Tobacco Control Research and Education.

While e-cigarettes deliver lower levels of carcinogens than conventional cigarettes, they also expose users to high levels of ultrafine particles and



other toxins that have been linked to increased risks of cardiovascular and noncancerous lung diseases – which account for more than half of all smoking-related deaths. The new study provides the first evidence of e-cigarettes' substantial impact on human health, indicating that they may be more dangerous than previously thought.

But, adds Glantz, who is also the American Legacy Foundation Professor of Tobacco Control, the results aren't all doom and gloom: “The good news is that the risk of heart attack starts to drop immediately after you stop smoking.”

Doctors Fail to Flag for Concussion Follow-Up

Football players aren't the only ones who should be worried about blows to the head.

As evidence builds about long-term effects linked to concussions, a nationwide study led by UCSF and the University of Southern California found that too many concussion patients fail to get critical follow-up treatment. The study followed patients who were seen at top-level trauma centers immediately after their injury. Less than half of them saw a physician or other medical provider again within the next three months. Worse, even patients who exhibited serious signs and symptoms received no subsequent care.

The lack of follow-up is concerning because patients can experience adverse and debilitating symptoms for a very long time, say the researchers.



Geoffrey Manley,
chief of
neurosurgery
at Zuckerberg
San Francisco
General

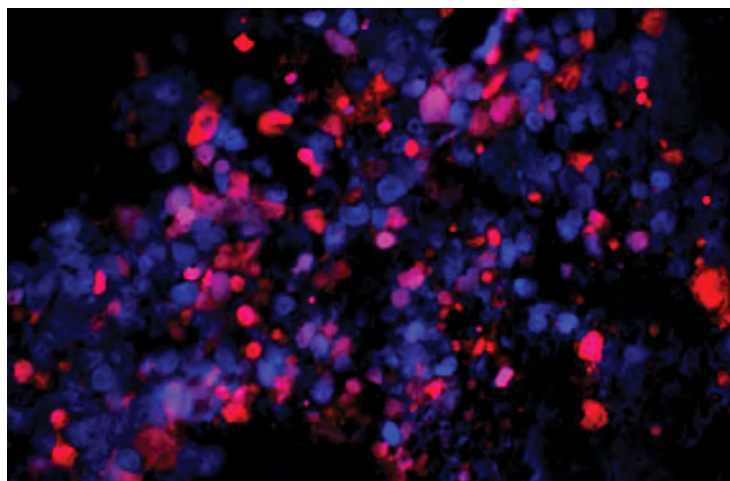


About 2.8 million people are treated for concussions and other more serious forms of traumatic brain injury (TBI) in U.S. emergency rooms every year. An expanding corpus of research shows that TBIs are associated with an elevated risk of neurodegenerative and psychiatric disorders. Two recently published UCSF studies found links between concussion and Parkinson's disease and between concussion and dementia.

"This is a public health crisis that is being overlooked," says the study's co-author, Geoffrey Manley, MD, PhD, a professor of neurological surgery and a member of the UCSF Weill Institute for Neurosciences. "If physicians did not follow up on patients with diabetes and heart disease, there would be accusations of malpractice. For too many patients, concussion is being treated as a minor injury."

A Self-Destruct Button for Prostate Cancer

UCSF researchers have discovered a new line of attack against treatment-resistant metastatic prostate cancer.



Analysis of hundreds of human prostate tumors revealed that the most aggressive cancers depend on a built-in cellular stress response to put a brake on their own turbo-charged growth process. Experiments in mice and with human cells showed that blocking this stress response genetically and with an experimental drug causes prostate cancer cells (in red in the image) to self-destruct, while leaving normal cells unaffected.

"We have learned that cancer cells become 'addicted' to protein synthesis to fuel their need for high-speed growth," says senior author Davide Ruggero, PhD, the Helen Diller Family Professor of Basic Research in Urologic Cancer. "But," he continues, "this dependence is also a liability: too much protein synthesis can become toxic."

Prostate cancer is the second leading cause of cancer death for men in the United States. More than one man in nine will be diagnosed with the disease in his lifetime, and one in 41 will die of it, according to the American Cancer Society.

"This is beautiful scientific work that could lead to urgently needed novel treatment strategies for men with very advanced prostate cancer," observes renowned prostate cancer surgeon Peter Carroll, MD, MPH, a co-author of the paper. Carroll chairs the Department of Urology and is the Derr-Chevron Distinguished Professor and the Taube Family Distinguished Professor.

We Left Our Homes for a Higher Calling

Then the travel ban brought isolation and uncertainty

By Hani Goodarzi

In a closely watched 5-4 decision, the U.S. Supreme Court recently sided with President Donald Trump and allowed the third version of his executive order on immigration, referred to as the travel ban, to go into effect.

Thousands of students from countries affected by the travel ban – people who already had limited access to parents, relatives, and longtime friends – have since been thrown into further uncertainty and isolation. Moreover, the reimposition of sanctions on Iran is obstructing the ability of Iranian students to get financial support from their parents. In coming months and years, students affected by this ban on travel from five Muslim-majority countries, plus North Korea and Venezuela, will need immense support from their home countries to stay sane and carry on.

I know because not long ago, I was one of those students. I came to the United States in 2006 to enter the molecular biology graduate program at Princeton. At that time, the National Security Entry-Exit Registration System, known as the Muslim registry, was in effect. After months of administrative processing, I was issued a single-entry visa valid for three months, because I am Iranian. This meant that while I could legally stay in the U.S. during my studies, I needed to reapply for a new visa – a process that could take months – every time I left the country. In practice, going back home was not an option since, like most STEM students, I was tied to my bench. I didn't see my parents again until six years later, after I became a permanent resident. I am an only child, so I believe this was harder on my parents than it was on me, as I was surrounded by close friends and was engaged in meaningful research to combat cancer.

The same administrative processing hurdles limited my parents' ability to travel to the U.S. to visit me – even before the institution of the travel ban. Now, even occasional visits are impossible. The de facto consequence of this policy is years of forced isolation for thousands of students and scholars.

When I was 20 years old, I felt invincible. I was ready to make sacrifices without fully understanding the depth of their consequences. I saw friends decide to go to schools in countries other than the U.S. so they could visit their families back home more often. But from my perspective, they were weak; they were not committed enough. Back then, a graduate degree from a top-notch school felt to me as if it was worth the six years of separation.

But it did not take me long to realize that I had grossly underestimated how much I depended on the emotional support of my family and childhood friends. With every birthday celebrated without them, with every wedding I missed, with every death in the family, I felt more and more isolated. I now lead a cancer research lab at one of the foremost institutions in the world, surrounded by some of the world's brightest minds, many of them longtime heroes. I have achieved the goals set by my younger self many times over. But even now, I catch myself wondering, in passing moments, if it's all worth it.

My goal is to put in perspective the challenges that many among us are facing because of this ruling. Numerous students, postdocs, and faculty will be under increasing pressure in the coming months to take stock of how this policy will impact their lives and careers. Some may even choose to forgo their current positions in the U.S. and seek opportunities elsewhere.

I do not yet see a clear path ahead. Nevertheless, I am confident that together we can find effective, albeit perhaps limited, solutions that cushion the blow for those affected by this ban. My optimism stems from the truly heartwarming support I've received from my colleagues and

the broader UCSF community. I hope that by sharing my story at a time like this, I can put a spotlight on the thousands of students who have left their homes to come to this country in pursuit of a higher calling. This is not my story alone. This is the story of many thousands of students from high-risk countries who have left their homes to seek a better education, a better life, and an opportunity to better serve humanity. In our capacity as educators, it is on us to step up and protect those who need it most.

Hani Goodarzi, PhD (below), is an assistant professor of biochemistry and biophysics and of urology and a member of the Helen Diller Family Comprehensive Cancer Center at UCSF.



Moral Medicine

Barbara Koenig, PhD '88, is leading a prodigious effort to help UCSF faculty and students navigate the ethical challenges posed by medicine's ever-expanding technological prowess. A medical anthropologist who started her career as a pediatric nurse, Koenig spent 20 years developing and leading bioethics programs at Stanford and the Mayo Clinic before returning to UCSF and, in 2016, launching the Bioethics Program in the School of Nursing's Institute for Health and Aging.

What big ethics questions is UCSF facing?

Here in the Bay Area and at UCSF, we are often on the cutting edge of innovative medical technologies like gene therapy and prenatal surgery. What are the limits in keeping our patients alive? How do we negotiate among competing duties: providing compassionate clinical care, meeting our teaching responsibilities, and partnering with for-profit biotech and pharmaceutical industries? What are our obligations – to our patients, the public, and the future of medicine – when it comes to sharing patient data? How should we administer physician aid in dying, which is now legal in California?

Why is it important to build a strong bioethics program?

Our clinicians are working with very ill patients, and caring for suffering patients often leads to severe moral distress. We have to support these clinicians by developing our internal vision for professional ethics and providing guidance about ethical behavior. We're creating a robust curriculum and sponsoring speakers, grand rounds, and a book club to build the intellectual community. Our course on responsible conduct of research is something all NIH-funded trainees are required to take. We also work with the UCSF Clinical Ethics Committee, which provides consults for people who have clinical ethics questions, and we run a research consultation service for those thinking through the design of a clinical trial or study. This is huge. If we do it right, we will be creating the moral conscience of the institution.



How do you define ethics? Is it about rules, or values, or goodness, or all of these?

This is not about personal values. We're talking about what constitutes the nature of good and virtuous clinical practice. The classic definition of biomedical ethics is a balance between the patient's wishes, beneficent practice, nonmaleficence ("do no harm"), and social justice. But some of the most challenging problems in health care require greater sophistication. There is no one, single guiding principle. It cannot be a utilitarian calculus, like number of life-years saved. Ethics must be based on caring relationships and virtuous practice.

How did you first get interested in ethics?

My work as a nurse made me aware of all these ethical questions. As a pediatric nurse, I had the experience of caring for a child who was so ill he needed two nurses to operate all the equipment keeping him alive. Like many clinicians, I've had the experience of patients begging me to help them die. I believe it is important to be a good "midwife" to the dying, but I'm still struggling, personally, with physician aid in dying. I believe it's more important to have universal health care in place first so that people without good medical coverage won't try to seek aid in dying because they can't get good palliative care.

What ethics issues are raised by gene research and therapy?

A good example of the questions we face is whether we should conduct genome sequencing on every newborn baby. I served as co-editor of an NIH-funded report on this issue that was recently published by the Hastings Center, a nonprofit bioethics research institute. We concluded that while testing makes sense for sick babies, it's not a good idea for healthy newborns because it could cause parents to worry needlessly. Offering guidance on these questions is important; our report offered concrete recommendations for practitioners.


What guidelines are being developed for sharing patient data?

As a public university, we have an obligation to share our extensive patient data because they drive improvements in basic research and health care delivery for the common good. I'm part of the UC President's Task Force on Health Data Governance, which includes representatives from all of UC's medical campuses. We're working on a data management strategy that engages patients and ensures the security of their data. This is consistent with UC's public mission, and we hope it will serve as a model for other academic centers.


— Patricia Meagher

BIOETHICS IN THE TRENCHES


Facing ethics questions in UCSF's clinics, labs, and classrooms

 "The boy's mother had witnessed death before, and she knew how ugly it could be. After her son's diagnosis, she decided never to subject him to the suffering she had witnessed. Even with therapy, she knew his chance of survival was minimal, so she decided against it. She knew what was right for her family. But we always gave therapy. Always. Our distress with her decision was palpable. Returning to our ethical framework — remembering that we honor parental authority, that we balance beneficence and nonmaleficence — helped steady our reaction. It reminded us that our instincts to treat are not always in the best interest of our patients. It revealed that this mother's decision was not merely ethically just, it was incredibly courageous and loving."

— *Efrat Lelkes, MD, Assistant Professor, Pediatric Critical Care and Pediatric Palliative Care*

 "When we're trying to diagnose severe pediatric disorders, we sequence the child's exome to look for a genetic cause. We also sequence the parents to determine what the parents may have transmitted to their child. In the process, we might get incidental findings; maybe the child has a BRCA1 mutation, which is a risk factor for breast cancer, and we can usually tell which parent is the carrier. So what do we do? Do we tell the parents? This generated a significant ethics discussion. We decided that, because the intent of the test was to diagnose the child, we are not obligated to share those findings, although they might be of potential benefit to the parents. Now we include a section on the consent form about secondary findings and ask the parents to indicate before we start testing whether they want to receive any such information."

— *Neil Risch, PhD, Lamond Family Foundation Distinguished Professor in Human Genetics; Director, Institute for Human Genetics*

 "One of the first patients I interviewed as a medical student came to the emergency room with a collapsed lung, known as pneumothorax. The attending physician had already examined and diagnosed him and, while waiting for transport to the hospital, the patient generously agreed to let me perform my own lung exam so I could become more familiar with pneumothorax. I had misgivings because I knew the exam would be painful without adding value to his care. On the other hand, I recognized my responsibility to future patients and was eager to further my knowledge of pneumothorax, a life-threatening emergency. I resolved my dilemma by letting the patient know that we could stop the exam at any time, thereby respecting his autonomy without undermining my ability to approach these learning opportunities with confidence."

— *Michael Sadighian, second-year medical student; coordinator, Bioethics Interest Group*



DECODING

THE

MYSTERY

OF

THE

SUPER-AGER

WHY DO SOME OF US SEEM IMMUNE TO THE RAVAGES OF TIME?

BY ADAM PIORE

It was the kind of case no traditional medical textbook could explain. The subject – let’s call him Peter Green – was a white male in his late 80s, enrolled in longitudinal studies of the elderly at the UCSF Memory and Aging Center. Green’s brain scans “were not pretty,” recalls Joel Kramer, PsyD, who directs the center’s neuropsychology program. His brain had begun to atrophy, and its white matter – composed of long bundles of nerve cells that carry signals from one area to another – were shot through with dead patches, suggesting that Green had suffered the kind of ministrokes often associated with cognitive decline.

Yet by all behavioral measures, Green was thriving. His cognitive test scores were impeccable and his ability to function in the world remained high.

“If you look at his cognition and level of functioning, it not only remains high – it hasn’t changed at all in years,” Kramer says. What was it about Green, Kramer wondered, that set him apart from his peers with similar brain scans, who seemed to have been waylaid by the ravages of time?

When Kramer finally met the study subject in person, the neurologist was struck by Green’s dynamism and sunny outlook on life. He told Kramer he volunteered in the community, was constantly busy with projects and organizations, and remained close to his family. He shared how grateful he was for what he had and really seemed to be enjoying his golden years.

“He talked about how his attitude toward life is one of embracing it – not getting stressed out by the little things and valuing the importance of relationships,” Kramer says. “I was so impressed. It was inspiring.”

Kramer has a name for people like this vigorous, dynamic octogenarian: “super-agers.” In recent years, he’s become increasingly fascinated by their qualities and has set out to solve the mystery of their success.

“There are some suggestions that people who are more optimistic age better than people who aren’t,” Kramer says, pointing to Peter Green as Exhibit A. “We’re just starting to look at these personality traits and how they influence aging.”

For decades, those studying the science of aging have devoted most of their time to trying to understand what goes wrong as we get older, what risk factors predispose us to disease, and how we might better diagnose and treat it. But in recent years, a growing number of researchers at UCSF and elsewhere have turned their attention to a separate but related series of questions: What is it that allows some older people to thrive? What is there to learn from the most resilient and functional senior citizens among us? And how might we apply that knowledge to everyone else to promote healthy aging?

Though the approaches UCSF researchers are taking to answer these questions vary – from studying large cohorts of elderly patients, to measuring telomeres, to analyzing components in the blood of variously aged mice – many of them have begun to converge on an optimistic conclusion.

“WHEN WE SEE
DECLINES IN MEMORY
AND OTHER SKILLS,
PEOPLE TEND TO THINK
THAT’S PART OF NORMAL
AGING. IT’S NOT.”
– JOEL KRAMER



Joel Kramer, a professor of neurology, is studying how personality traits might influence aging.

“As we get older, when we see declines in memory and other skills, people tend to think that’s part of normal aging,” Kramer says. “It’s not. It doesn’t have to be that way.”

STRESS CAN MAKE US OLDER

Elissa Epel, PhD, a professor of psychology who co-directs the UCSF Aging, Metabolism, and Emotions Center, believes one’s chronological age and biological age do not always align. She is trying to understand what makes some of us more resilient than others, and one of the answers seems to be stress.

“The biology of aging and the biology of stress are intimate friends, and they talk to each other and influence each other,” she says. “The greater the feelings of chronic stress, the greater the signs of aging in cells.”

Epel is studying participants under almost constant stress: family members who are caring for a child with a chronic condition or a spouse with dementia. As one proxy for biological age, Epel monitors the length of individuals’ telomeres, or caps on the ends of chromosomes, which shorten as we get older.

When our telomeres get too short, our cells are no longer able to divide. It becomes harder for our bodies to replenish tissues, and our chances of developing chronic diseases increase, Epel explains. Short telomeres in midlife predict an early onset of cardiovascular disease, diabetes, dementia, some cancers, and many other diseases often associated with aging.

Chronic stress, she and others have found, can lead to a buildup of proinflammatory factors called cytokines, which mobilize our immune system to release a series of chemicals

that, though important in fighting infection, can over time harm the body's own cells. Chronic stress can impair mitochondria, the energy centers of our cells, accelerate the epigenetic clock (a measure of cellular age based on the methylation patterns of genes), and prematurely shorten our chromosomes' telomeres.

But Epel has found that there are things we can do to counteract the toxic effects of stress and slow down the aging process.

"The big story is that there are so many differences among caregivers in the way that they're responding to their life situation," Epel says. "What's emerged is how much our mental filter – how we see the world – determines our reality and how much we will suffer when we find ourselves in difficult situations in life."

It's possible to modify that filter through consciously cultivating gratitude and a mindful response to stress, Epel says. This sounds much like the mindset of the "super-ager" that Kramer has observed. Social support is one of the largest factors protecting us from stress. Caregivers who have a greater number of positive emotional connections appear to be protected from much of the damage caused by stress. In addition, meditation, exercise, and an anti-inflammatory diet can reduce and possibly reverse some effects of aging.

"While extreme biohacks are super interesting, most of them are probably not feasible and not healthy in the long run," she says. "But lifestyle interventions are a form of biohacking that is feasible, safe, and reliable. Our biological aging is more under our control than we think. If we can make small changes and maintain them over years and years, our cells will be listening and maintaining their resiliency and health."

She adds that context also plays a role. Culture and environment – at home, work, and in neighborhoods – are important components in the ability of individuals to maintain lifestyle interventions over the long run. She notes that while extended health span is feasible and already unfolding for many of those with higher education, so far there are very slim gains in health span for minorities and those with strained socioeconomic resources.

UCSF is working to modify the culture in ways that support such healthy changes on campus, she notes, pointing to the Stress Free UC program, a daily meditation app that is free to any UC staff member: stressfreeuc.org.

AGING – AND YOUTH – ARE LITERALLY IN OUR BLOOD

While Epel is zooming out to explore how the mind-body connection might promote healthy aging, UC San Francisco's Saul Villeda, PhD, is zooming in, examining how microscopic, cellular messages that travel through our bloodstream might impact geriatric health.



Elissa Epel, a professor of psychology, says our biological aging is more under our control than we think.



Saul Villeda, an assistant professor of anatomy, showed that infusing young blood into older mice reversed signs of age-related decline.

Villeda, an assistant professor of anatomy, oversees a group of 12 researchers looking into mechanisms of brain aging and rejuvenation. His experiments sound a little like science fiction. In 2014, Villeda published a study in *Nature Medicine* showing that infusing the blood of young mice into older mice could significantly reverse signs of age-related cognitive decline – that is, geriatric mice infused with young mouse plasma were better able to both recall the way through a maze and find a specific location. Conversely, younger mice injected with older blood experienced accelerated symptoms of aging.

What is it about young blood that can have such a profound effect? Using a method known as parabiosis, connecting the circulatory systems between older and young mice, Villeda found that the young blood caused the number of stem cells in the brains of older mice to increase and the number of neural connections to spike by 20 percent.

Earlier this year, he published a study demonstrating that infusing the young blood also caused a spike in an enzyme called TET2 in areas of the brain associated with learning and memory. The research team, led by one of Villeda's postdocs, Geraldine Gontier, PhD, demonstrated not only that TET2 levels decline with age but that restoring the enzyme to youthful levels improved memory in healthy adult mice.

The stimulatory effect of young blood, Villeda says, likely results from a handful of factors acting together. (He also points to another factor that seems to play a role in the magical properties of young blood – a protein called metalloproteinase that is involved in remodeling the structural components that hold our cells together and give them their shape.)

Meanwhile, Villeda has also isolated factors in old blood that accelerate aging. Blood from mice who are the equivalent of 65 human years contains cellular signaling agents that he says promote inflammation. These agents play what he calls a "huge role" not just in cognitive declines but also in muscle and immune-related deterioration – results that are consistent with those found by Epel.

By continuing to decode these cellular components, Villeda believes we may someday be able to harness what he and others are learning in order to create new medicines that rather than target single diseases, target some of the underlying factors that cause diseases of aging in general.

This idea, of making therapies that treat aging in the same way we treat other diseases, says Villeda, is becoming "more mainstream."

"We don't think of aging as final anymore. We're basically maintaining a youthful state for longer." Even 15 years ago, Villeda continues, "if you told someone, 'I can keep you healthy until you're 85 and you won't get cardiovascular

FOUR STRATEGIES FOR AGING WELL



1. EMBRACE AGING

Many of us experience a better balance between positive and negative emotions as we age, notes Elissa Epel, PhD, co-director of the UCSF Aging, Metabolism, and Emotions Center.

“When we’re older, we seek positive situations in our life much more and cut out things we don’t like. We take more control of our environment,” she says.

What’s more, the wisdom that often comes with age may be related to structural changes in older brains. Bruce Miller, MD, director of UCSF’s Memory and Aging Center, points to recent work showing that brain circuits involved in altruism, wisdom, and thinking about other people are shaped based on the cumulative experiences of our lives. One’s ability to consciously control emotions improves as this circuitry increases.

This is why so many people can think of an older person who has had a profound influence on them, says Miller. “It’s because of the brains of elders. We are more prosocial. We are more likely to give to people in need than younger people. This is not a huge surprise ... but we’re now able to think of the biology of this. We really need our elders.”



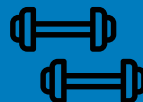
2. QUIT THE NEGATIVITY

Negativity and fear associated with aging often overshadow the positive aspects of growing older. Ironically, this fact can have its own damaging consequences.

“We hold these tremendously negative stereotypes about aging, and these start from when we’re really young,” Epel explains. “By the time we’re older, these are actually having a negative effect on our health.”

When we believe that aging means we’re “going to be suffering and frail and dependent,” Epel says, “we don’t heal as quickly when we break a hip. We’re more likely to get dementia, regardless of whether we have the gene associated with Alzheimer’s. And we don’t live as long.”

The most obvious explanation is that it’s a self-fulfilling prophecy: When we harbor the belief that we can’t control our rate of aging, we develop a fatalistic attitude and engage in fewer healthy behaviors. But there may be something even more insidious at work. Studies show that negative attitudes about aging can actually cause us to become more stress reactive and less stress resilient – triggering biochemical cascades that may actually *accelerate* aging.



3. MOVE MORE

The positive effects of physical activity on cognitive functioning in older adults are well documented. Exercise leads to the production of more brain cells, increases cardiovascular health, and promotes a sense of well-being. It also appears to be highly correlated with cognitive processing speed, says Joel Kramer, PsyD, a professor of neuropsychology who has spent more than a decade studying the super-agers among us. In a 2017 study, Kramer and his team showed that exercise may even exert a protective effect against cognitive decline in those carrying genes that place them at a greater risk for Alzheimer’s.

Meanwhile, in a 2018 study, a team led by Eli Puterman, PhD, examined a cohort of 68 elderly individuals who were caring for family members with dementia. These caregivers were under high stress, had high levels of depressive symptoms, and had sedentary lifestyles. The study

encouraged participants to exercise for 40 minutes, three to five times per week, for six months. At the end of that period, participants had lengthened their telomeres, a biomarker associated with longevity.



4. MEDITATE

Epel and several collaborators recruited 28 participants enrolled in a California meditation retreat to undergo extensive testing. The researchers monitored markers associated with biological age (including telomere length, gene expression, and more) and also tracked participants’ anxiety, depression, and personality traits over the course of the intensive, one-month meditation retreat.

The participants meditated for extended periods under the guidance of experienced practitioners, refrained from speaking, and were encouraged to treat all daily activities as “opportunities to attend to their ongoing mental experience with open and reflexive awareness.”

At the end of the retreat, the participants’ telomere length had increased significantly, and participants with the highest initial levels of anxiety and depression showed the most dramatic changes over the course of the study.

What’s next? Epel’s team, with a \$1.2 million gift from the John W. Brick Foundation for Mental Health, will study how natural treatments – including mindfulness meditation, high-intensity interval training exercise, and different breathing techniques – impact mood, health, and biological aging. At the time of publication, they are seeking women participants who could benefit from these interventions. More information and enrollment requirements are at www.stressresilience.net.

disease or Alzheimer's, and all you have to do is take this pill,' people would probably have been looking at you a little strange."

But attitudes have begun to change. "If you tell them, 'We understand the molecular mechanisms that are driving certain aspects of aging, and we can target them,'" he says, "it becomes much more understandable to people."

THERE IS STILL MORE TO LEARN

Joel Kramer has been following some of his "super-agers" for more than a decade. They now number in the dozens and are part of a far larger cohort of subjects ranging in age from 60 to 95.

At least every two years, each subject comes in to answer questions about their lifestyle and to undergo a battery of tests – of their cognitive function, blood composition, brain volume, and a wide array of other factors associated with aging and their ability to function in the world.

The study continues to produce reams of data, much of which Kramer and his colleagues have barely begun to analyze.

But a complicated picture has started to emerge, one highlighting multiple factors that interact to affect our ability to function. In March 2017, Kramer and his colleagues published the first of many planned studies exploring some of the characteristics that seem to be associated with cognitive and functional performance. They compared 17 "resilient agers," who exhibited fast cognitive processing speeds, to 56 "average agers" and 47 "sub-agers," whose cognitive processing speeds appeared to be slowing down.

Just as Epel and Villeda predicted, the resilient agers had lower levels of proinflammatory cytokines than the sub-agers. Anatomical differences may have also played a role in the differences among the cohorts. For example, the starting size of the brain's corpus callosum, a thick band of nerve fibers connecting the two sides of the brain, was larger in resilient agers than in sub-agers.

The lower levels of inflammation might be attributable in part to lifestyle choices – especially since this group self-reported higher levels of exercise.

In a study currently under review for publication, Kramer and his team found that the brains of those who ate a healthy Mediterranean-style diet were less likely to contain large amounts of a protein associated with Alzheimer's. One of his colleagues has found evidence that higher levels of mental activity are correlated with a growth in the connections between brain cells and with better cognitive processing speeds. Others suggest that sleep plays a crucial role in healthy aging.

"There's definitely a genetic component, which is very big," notes Kramer. "But these are all little hints that there are things we can do to improve our chances of better brain aging."

"OUR BIOLOGICAL AGING
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MAKE SMALL CHANGES AND
MAINTAIN THEM OVER YEARS,
OUR CELLS WILL BE LISTENING."

– ELISSA EPEL



Bruce Miller, the Clausen Distinguished Professor of Neurology, says advances in imaging have helped decode the biology of older brains.

The paradigm shifts emerging from the new science are already beginning to have an impact in the clinic.

Bruce Miller, MD, the Clausen Distinguished Professor of Neurology and director of UCSF's Memory and Aging Center, is collaborating with Kramer on the healthy aging study. Miller, Kramer, Epel, and Villeda are all members of the UCSF Weill Institute for Neurosciences as well. Miller notes that when he first arrived at UCSF in 1998, the field in general was "very nihilistic." Age-associated decline was seen as inevitable. Since then, however, that assumption has changed.

"I think imaging in particular has advanced in a way to allow us to do these sorts of studies that we never could have done before – and say, 'Wow, we now have these really clear biological markers in elderly populations, so we can now think about whether they're changing when we intervene.'"

The evidence is convincing that cardiovascular health, exercise, and low-fat diets can all make a positive difference, he says.

Kramer notes there's still more work to be done, however. "We clearly just started doing this," he says – but then adds that the study is already having an impact on at least one person: himself. "Having contact with so many of our older subjects who have maintained good brain health has really inspired me," Kramer says. "Even just the simple fact that they exist is inspiring. It's an exciting time."



←
Theo Roth, an MD-PhD student, is developing techniques to reprogram immune cells to treat cancer and HIV infection. “Genome surgery isn’t just about repairing DNA,” he says. “We also want to put new sequences into cells that impart new therapeutic functions.”

THE FIRST GENOME SURGEONS



Scientists have built tools that can cheaply and easily edit DNA. Now they are preparing to bring them into the clinic to cure disease.

By Ariel Bleicher

One afternoon in July, deep within the labyrinthine halls of the Medical Sciences Building at UCSF's hilltop campus on Parnassus Avenue, the laboratory of Alex Marson, MD, PhD, is buzzing. Doors clap. Gloves snap. Keyboards clack. Cells incubate in nutrient baths the color of Kool-Aid while machines resembling rice cookers spin mixtures of molecules, separating large from small. Every now and then, a printer whirs with notes for a new experiment, like a lunch order arriving in a restaurant kitchen.

Theo Roth, an MD-PhD student, opens a deep freezer, releasing an icy cloud. Here, amid frosted boxes stacked on frosted shelves, is the impetus for all this activity – the reason Roth and Marson and their colleagues at UCSF and elsewhere have begun to suspect, with no small amount of excitement, that they are in the vanguard of a new era in medicine.

Roth pulls out a box and lifts from it a transparent plastic vial no taller than a toothpaste cap. Inside, he explains, are billions of intricately folded, ribbon-like molecules: proteins known as Cas9. When linked to other molecules called guide RNAs, the Cas9 proteins transform into ...

"... the magic CRISPR system," Roth says, holding the vial up to the light.

Its contents look like ... well, nothing. "Just another clear liquid," Roth jests – because as he well knows, these molecules' humble appearance belies a singular and extraordinary power.



**Publications
about CRISPR**
In 2012: 139
In 2017: 3,080
Source: PubMed



**Rare Genetic
Diseases**
Known: 6,259
Curable: 0

Source: Online Mendelian
Inheritance in Man

The Coming CRISPR Cures

If you've heard of CRISPR (pronounced "crisper"), a hot topic in science circles nowadays, you've likely encountered a dizzying array of definitions and divinations. Is CRISPR a therapy? A revolution? A pair of genetic scissors? A text editor? A genesis engine? A gateway to designer babies? And what does that catchy acronym – which stands for "clustered regularly interspaced short palindromic repeats" – even mean?

Put simply, CRISPR is a tool. In fact, it is many tools – more precisely described as CRISPR systems – exquisitely engineered for operating on life's tiniest anatomy: DNA, the substance of genes. These tools aren't the first of their kind, but they are by far the most exacting, the cheapest, and the easiest to use. Dispatched into living cells, they can be made to manipulate any gene in any tissue in any organism, whether microbe, mouse, or monkey.

Or human. Just six years after the discovery of CRISPR technology, hundreds of research labs around the world are now using it to study patients' cells and to create animal models of human diseases – from common illnesses to inherited disorders so rare that they may affect only a few families. This fast-growing body of research has proven a boon to medical science, showing how DNA – a spiraling

chain of chemical bases strung together like rungs on a ladder – keeps us alive and healthy, and how even subtle changes in this code can make us sick.

But for physician-scientists like Marson and young trainees like Roth, the ascendancy of CRISPR systems raises an even grander hope: If these tools can illuminate the causes of disease in the laboratory, why not bring them into the clinic to treat patients?

What CRISPR scientists envision – the future they are now preparing for – is a whole new field of medicine. They even have a name for this nascent specialty: genome surgery. Just as today's surgeons use steel instruments to excise tumors,

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– JENNIFER DOUDNA

repair blood vessels, or transplant kidneys, tomorrow's genome surgeons could use CRISPR systems to remove one faulty gene, correct another, or replace a third – thereby curing genetic diseases at their source.

"Imagine a world where people go to the doctor, and they get their genome sequenced and learn they have a genetic disorder," says Jennifer Doudna, PhD, who famously pioneered the first CRISPR applications in 2012. "And instead of telling them they need to live with that disorder, we have the technology that can actually treat them – potentially even cure them."

It's a lofty vision but one that may be within reach. In 2014, Doudna – who is a professor of chemistry and of molecular and cell biology at UC Berkeley and a senior investigator at the Gladstone Institutes, an independent research institute affiliated with UCSF – helped found the Innovative Genomics Institute (IGI), a partnership between UC Berkeley and UCSF to apply CRISPR systems to improving human health. (Its mission later expanded to also encompass food security and environmental sustainability.) Since then, teams of

How to Operate on DNA

Future genome surgeons will choose from a grab bag of molecular instruments to perform cellular procedures unique to each patient and disease. Here's how:

1 MAKE A MOLECULAR MAP OF THE FAULTY DNA



2 PAIR WITH A SURGICAL PROTEIN TO CREATE A CRISPR SYSTEM

dCas9 binds to DNA but does not cut.

Cas9 binds to and cuts DNA.



Activators and repressors dial gene activity up or down.

Base editors change only single letters in the DNA code.



Fluorescent tags track genes' behavior.

3 ADD OPTIONAL MOLECULAR ATTACHMENTS

4 DELIVER TO A CELL

Use a cut to disable a disease-causing gene.



Provide a new gene template. The cell will repair the cut with this new code, thereby restoring a lost function or gaining a new one.

Genome Editing: A 50-Year Quest

Scientists began searching for ways to edit genomes in the 1960s. Working in test tubes, researchers at UCSF and Stanford bombarded DNA with various combinations of molecular widgets, all borrowed from bacteria. Some of these widgets slice apart DNA bases like miniature scythes; others fasten them together like glue.

In 1972, after a few years of trial and error – much of which took place in the UCSF laboratory of Herbert Boyer, PhD, then an assistant professor who would go on to co-found the biotechnology giant Genentech – the researchers eventually landed on a recipe for cutting and pasting DNA. For the first time, it was possible to mix and match genes to create hybrid sequences – called recombinant DNA – that had never before existed.

You could, let's say, take a virus like HIV, delete the genes that make it virulent, and splice in a gene from a human cell. You could then unleash copies of your recombinant virus in the cells of a patient with a diseased copy of this gene. The viruses would naturally insert the new gene into the cells' DNA, where it could compensate for its native, mutant twin and alleviate the disease's symptoms.

This scenario is the basis of gene therapy – imbuing cells with healthy genes to make up for sick ones. It's a promising approach. First tried in 1989, gene therapy progressed in fits and starts, plagued by unexpected setbacks – most notably the death of a patient in 1999. Those early setbacks, however, have been largely worked out, and “gene therapy 2.0” is now being tested in hundreds of clinical trials across the U.S., including several at UCSF clinics to treat sickle cell disease, beta thalassemia (a rare blood disorder),

severe combined immunodeficiency syndrome (sometimes called “bubble boy disease”), and Parkinson's disease.

Still, the technology has its drawbacks. It's really more of a patch kit than a repair shop, and an imperfect one at that. Because gene therapy adds a new gene at an unpredictable spot in a cell's genome, the gene's fate isn't a sure thing. Genes, after all, don't work in isolation. They lie amid various DNA segments called regulatory DNA, which tell the cell how to read the code, much like notations on a music score. Consequently, a therapy gene – randomly inserted into the genome by a virus – might land near regulatory DNA that silences it, rendering it useless. Worse, it might disrupt a healthy gene or turn on a gene that causes cancer.

In the early 2000s, scientists went searching for tools they could better control. By cobbling together parts of natural proteins, they found they could synthesize artificial proteins able to target mutations at desired locations in a genome. One of the more capable creations, called a zinc-finger nuclease (ZFN), has already made its way into clinical trials. The first test in a human patient was led by Paul Hartz, MD, at UCSF Benioff Children's Hospital Oakland – in partnership with Richmond, Calif.-based Sangamo Therapeutics – in 2017.

Engineering proteins, however, is no small feat. It takes weeks or even months to adapt a ZFN to target just one of the many thousands of known disease-causing mutations. The process is simply too time-consuming and costly to be of practical use in treating the vast majority of genetic diseases.

For nearly a decade, researchers struggled to find a better way – until, in 2012, CRISPR came along.

researchers and clinicians in the Bay Area alone – many of them funded through IGI – have begun to work toward new CRISPR surgeries that could treat an array of diseases, including genetic disorders of the eye, nerves, kidneys, blood, and immune system. [See “San Francisco Area Genome Surgery Projects,” p. 27.]

“The possibilities are mind-boggling,” says Marson, an associate professor of microbiology and immunology and the scientific director of biomedicine at the IGI. He, together with Roth and others, is developing CRISPR-based techniques aimed at reprogramming patients' own immune cells to kill cancer and to ward off HIV. The day when treatments like these enter the clinic may not be so far off.

“Genome surgery is not science fiction anymore,” Doudna says. “It's really coming down the pike.”

New Hope For Rare Disorders

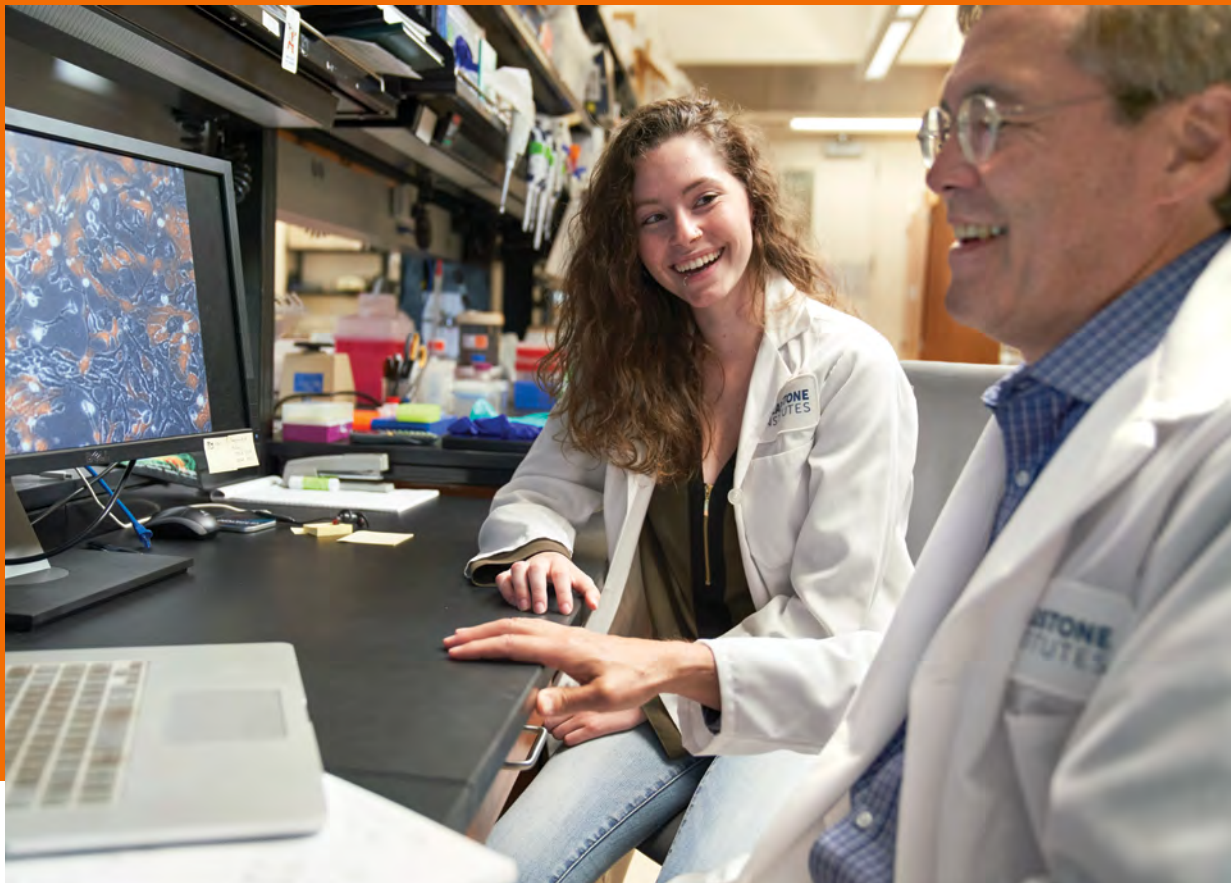
While Marson's team busies itself remodeling immune cells, a few miles away at the Gladstone Institutes, on UCSF's Mission Bay campus, a different sort of genome surgery is underway. There, in the laboratory of senior investigator Bruce Conklin, MD – a UCSF professor of medicine and IGI's

“IT'S NICE TO REALIZE
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– DELANEY VAN RIPER

deputy director – the cells of 19-year-old Delaney Van Riper are undergoing experimental procedures that could one day cure her of a worsening disability.

Van Riper was born with a rare disease called Charcot-Marie-Tooth (CMT), one of more than 6,000 known genetic disorders that arise from specific variations in DNA. Such variations – called mutations – throw a wrench in a cell's protein production line, thus creating deviant or defunct molecules, like IKEA furniture assembled from garbled instructions. In some cases, a mutation in just one DNA base – out of the total 3 billion pairs of bases in the human genome – can wreak severe havoc.



PATIENT PIONEER

Nineteen-year-old Delaney Van Riper (left) donated her cells to the lab of Bruce Conklin, MD (right), so he can test DNA surgeries that aim to cure people like her who have rare genetic disorders. “Secretly, I do think it will work,” she says.

Van Riper’s mutation produces a miscreant protein that degrades her nerve cells’ ability to relay messages between her brain and her muscles, causing her to slowly lose control of her limbs. She was diagnosed at age 7, after her father, a genetic counselor, noticed that she wasn’t walking normally. By age 8, she wore leg braces, laughing along with the kids who called her Forrest Gump, “so they didn’t see me as a cripple.” By age 13, she struggled to hold a pencil.

“There are certain muscles I just don’t have anymore,” she says during a recent visit to the lab. She is seated at a conference table, where a dozen or so researchers from Conklin’s group have gathered to meet her, many of them for the first time.

The researchers know her cells intimately, however. They have isolated them from samples of her blood and nurtured them in petri dishes. They have doused these blood cells with a cocktail of genes that turns them into stem cells, undifferentiated cells that can grow indefinitely. Using another gene cocktail, they have coaxed the stem cells to become nerve cells like those at the root of Van Riper’s disease. They have examined these diseased nerve cells through microscopes, studied their troublesome mutation, and sent in CRISPR systems to try to remove it.

All the while, Conklin and his team have dreamed about a day when a physician might inject CRISPR molecules

directly into Van Riper’s spine to heal the nerve cells there; a day when the success of this pilot surgery will lead to more CRISPR operations for more diseases; a day when patients who once had no hope will come to San Francisco from all over the world to seek these treatments out.

Now the researchers want to know all about this dark-haired teen who wears black skinny jeans, Converse sneakers, and a lip-ring; who has trouble using her hands and sometimes stumbles over her feet but sits with exquisite posture; who speaks eloquently and vulnerably about the disease that once made her question who she is and inspired her to become a writer and a medical trailblazer.

“How does it feel to be part of this project?” someone asks.

“It’s nice to realize people are looking into a solution for people like me who don’t have any solutions,” Van Riper says. “I feel you really care.” She flashes a grin and adds, “I like nerds.”

“Do you worry about the risks?”

“I’ve lived long enough to have an experience of life with a disability. If something goes wrong, I don’t think it would be as scary as some people think. We can’t know until we do it. I’m fine being that person doing it.”

“You’re really brave.”

“I know it’s not a for-sure fix. Secretly, though, I do think it will work.”



↑ **CRISPR QUEEN**
Jennifer Doudna pioneered CRISPR technology in her lab at UC Berkeley in 2012.

So do many of Conklin's patient volunteers. Some, like Van Riper, have CMT; others have genetic mutations that cause Best disease, an eye disorder that leads to blindness.

Conklin's team is starting with these two rare diseases for several reasons. First, they each arise from well-known mutations in a single gene, making the CRISPR surgeries relatively simple to design. Second, they affect tissues where CRISPR systems can be easily administered and their effects easily measured. Third – and perhaps most important – these diseases are currently untreatable; any relief from their devastation is, for most patients, worth the potential risks (which may include, for instance, cuts in undesired parts of the genome).

"Almost universally, the first targets of genome surgery will be incurable diseases, where there is truly no other option," Conklin says. "If we can treat these, it will open the door to a new type of medicine."

An Unexpected Windfall

It's easy to see, even for the researchers involved, how the promise of genome surgery can sound like magic. Of course, the process is not magic at all but a very real, albeit exceptional, molecular operation that traces its origin to an unassuming source.

Starting in the 1980s, biologists studying bacteria and other microorganisms noticed strange regions of DNA in their genomes. Surprisingly, the regions contained segments that were palindromes – they read the same forward as backward – and that repeated at regular intervals, like books in which every paragraph begins with the word "RACECAR." Those oddities gave the segments their mouthful of a name: clustered regularly interspaced short palindromic repeats, soon shortened to CRISPRs.

Eventually, researchers determined that CRISPRs bookend pieces of DNA stolen from invading viruses, like frames around criminal mug shots. The whole DNA region serves as a kind of microbial defense force: Genes near the CRISPRs code for defender molecules, called CRISPR-associated (Cas) proteins, that execute viruses by chopping up their DNA; the viral mug shots, copied into RNA molecules that stick to the Cas proteins, serve as the defenders' guides.

For decades, CRISPR research remained a relatively obscure niche of biology. Then, in 2012, a team led by UC Berkeley's Doudna and Emmanuelle Charpentier, PhD, then of Sweden's Umeå University and now a director at the Max Planck Institute for Infection Biology in Berlin, published a paper that launched CRISPR to scientific fame.

The paper described how one particular Cas protein, Cas9, could be directed to cut not only bacteria-invading viruses but *any* piece of DNA, simply by changing Cas9's RNA guide. That ability – to create a specific DNA editor by supplying a specific RNA molecule – was revolutionary. RNA, after all, is easy to make in the lab. Scientists could therefore build a plethora of new Cas9-based tools in a fraction of the time and at a fraction of the cost of previous technologies. [See *"Genome Editing: A 50-Year Quest,"* p. 24.]

This discovery ignited a CRISPR frenzy. Around the world, labs quickly embraced the so-called CRISPR-Cas9 system, using it to cut out and splice genes into bacteria, fungi, plants, animals, and, of course, human cells. "It was just remarkable how fast it spread," Doudna recalls. Soon, researchers were rejiggering Cas9 to create CRISPR tools with more diverse abilities, thus expanding Cas9's scalpel into an array of surgical instruments. [See *"How to Operate on DNA,"* p. 23.]

In 2013, for instance, Doudna teamed up with several UCSF researchers – including Stanley Qi, PhD (now at Stanford); Luke Gilbert, PhD (the Goldberg-Benioff Professor); Jonathan Weissman, PhD; and Wendell Lim, PhD – to show that a mutated version of Cas9, called "dead" Cas9, or dCas9,

could bind to a DNA target but not cut it. This insight proved incredibly fruitful: By fusing various other molecules to dCas9, the team could use the resulting systems to dial up or dial down gene expression without altering the underlying DNA. “Now we had a volume switch,” says Weissman, a professor of cellular and molecular pharmacology and co-director of IGI.

Other labs soon found further add-ons: molecular tags to track genes’ behavior; molecular proofreaders to edit single bases; molecular shields to stop rogue cuts; molecular switches to allow remote control. “It was kind of amazing,” Weissman says. “In the course of just six years, we did everything we wanted and much more.”

The challenge now for genome surgeons is to find which combinations of CRISPR systems, in what order and under what conditions, will treat a particular patient with a particular disease safely and effectively.

On The Medical Frontier

Back in the Marson lab, Roth has mixed the ingredients for his “magic” CRISPR system in a flask and left them under heat to allow them to assemble. Now, using a syringe-like pipette, he sucks up the CRISPR molecules and divvies them, squirt by tiny squirt, among the wells of a honey-

NEW CRISPR SURGERIES COULD TREAT AN ARRAY OF DISEASES. “THE POSSIBILITIES ARE MIND-BOGGLING,” SAYS ALEX MARSON.

combed plate. There, he will test the system on human T cells – a type of immune cell – to see how well his surgical procedure works.

“In a clinical setting, this would be done by a robot,” he says, as if he’s already envisioning a day when all this tinkering – and tedious pipetting – will not only satisfy scientific curiosities but also save lives.

Next, he adds to the wells another ingredient: genes. These particular genes code for a protein called a synthetic T-cell receptor, or TCR. Perched on the surface of T cells like border guards, receptors detect toxic particles or pathogens entering the body, thereby instigating an immune attack. A synthetic TCR is a lab-made receptor designed specifically to

recognize cancer cells – in this case, some forms of melanoma. If all goes as Roth expects, the CRISPR system will splice the TCR genes into the T cells’ DNA precisely where he wants them, turning the cells into cancer-killing agents. (In 2017, the U.S. Food and Drug Administration approved two older-generation T-cell therapies that use non-CRISPR technologies, one for acute lymphoblastic leukemia and the other for advanced lymphomas.)

“Genome surgery isn’t just about repairing DNA,” Roth says, now pipetting the human T-cells into the test wells to mingle with the CRISPR molecules and the TCR genes. “We also want to put new sequences into cells that impart new therapeutic functions.”

Finally, he slides the entire well plate – with its motley crew of residents – into a breadbox-sized contraption: an electroporator. *Click, click, click* goes the electroporator, delivering a series of mild electric shocks. The shocks make the T cells’ sack-like membranes permeable, letting the CRISPR molecules and the TCR genes slip through. When at last the electroporator ejects the cells, Roth sets them in an incubator to warm.

A couple of days later, after the CRISPR system has had time to perform its tricks, he will analyze the data. He will determine, to his satisfaction, that they are “somewhat as we expected.” Then he will start preparing the next experimental run – one of hundreds he has done over the past year and will continue to do in the months to come – in the hope of making the procedure just a little easier, a little safer, a little more effective.

Like most genome surgery pioneers, he is cautiously optimistic that his efforts will pay off. The rapid rise of CRISPR technology, followed by early therapeutic progress, has given scientists and physicians alike reason to be hopeful – to “feel encouraged,” as Doudna says, “that this is something that in the next few years will be increasingly available to patients.”

At the same time, many important questions remain: How will physicians deliver CRISPR systems to hard-to-reach tissues such as the heart? How will they treat diseases with many underlying and interacting gene mutations? How will they educate patients about the risks and benefits? What exactly are the risks and benefits? What are the proper doses? How will these surgeries be regulated? Who will perform them? Who will pay for them? Who will have access to them?

“There’s plenty of work still to be done,” Roth says, speaking for the field as well as himself. He and his peers are like Apollo engineers – tweaking one more sensor, running one more simulation – before launching a space flight, with astronauts aboard, into the starry unknown.

Even before liftoff, CRISPR therapies are already a *pièce de résistance* – a testimony to just how far science has taken us and where it yet may lead.

San Francisco Area Genome Surgery Projects

CRISPR-based surgeries currently in development at UCSF, UC Berkeley, the Gladstone Institutes, and the Innovative Genomics Institute aim to treat the following conditions:

- Sickle Cell Disease (a blood disorder)
- Best Disease (an eye disorder)
- Charcot-Marie-Tooth (a neurodegenerative disorder)
- Severe Combined Immunodeficiency
- Cancer
- HIV Infection
- Autoimmune Disorders
- Polycystic Kidney Disease
- Obesity
- Hemophilia (a blood disorder)



When Ordinary Becomes Extraordinary

“I still remember my first steps after the accident,” says Matthew Wetschler, MD, who broke his neck while body surfing off the coast of San Francisco in 2017. Unconscious, he was pulled ashore and rushed to Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG), where he became the first person to undergo a new protocol for treating spinal cord injuries.

A key part of the protocol, pioneered by Sanjay Dhall, MD, a UCSF associate professor of neurological surgery and the director of spinal neurotrauma at ZSFG, is getting a patient into surgery as quickly as possible, ideally within 12 hours of an injury. The protocol also calls for raising the patient’s blood pressure to a

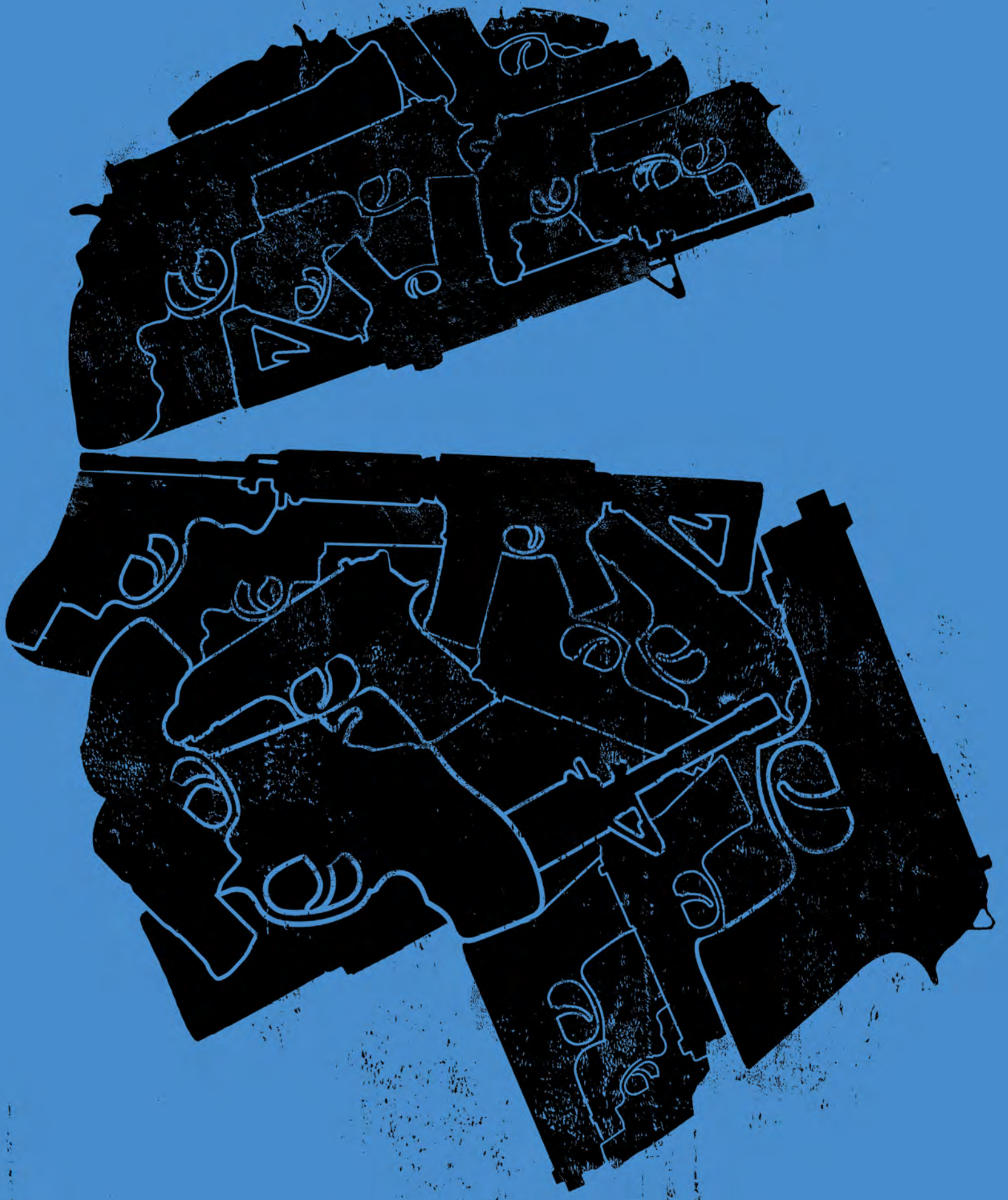
level that depends on his or her natural spinal pressure. This personalized care increases the likelihood of recovery while minimizing harm.

Wetschler, whose accident forced him to put aside his career in emergency medicine but has given him a chance to pursue art and motivational speaking, was walking again within two months of surgery. “When something so meaningful is taken from you, to get it back when it wasn’t certain is beautiful. It was one of the best gifts of my life,” he says.

One year later, surrounded by friends, he went surfing again for the first time. “The ocean has always been a place of solace and catharsis,” he says. “I can still appreciate its scale and majesty, while having great respect for its power.”

– Ariel Bleicher





BEYOND

THE BULLET

BREAKING THE CYCLE OF VIOLENCE

By Claire Conway

Jamal was in a good place. He was enrolled in a program that employed him while he was earning his high school equivalency degree. He enjoyed the work – doing landscaping all over the city. He had made good friends, he liked having money in his pocket, and he was doing something positive.

Until he was shot in the face.

Jamal, then 24 years old, was shopping for a shirt after work in downtown San Francisco when a car pulled up to the curb next to him. The window rolled down, and the passenger called his name. Jamal turned and walked toward the car. The bullet was probably already entering the barrel of the pistol when he caught a glimpse of the shooter – someone he had never seen before and hasn't seen since. The bullet tore Jamal's mouth from his face. An ambulance came, and the crew strapped him to a gurney. "I had to fight with the medics," Jamal recalls. "I was choking from the blood, and they were forcing me to lie on my back. I kept thinking, 'Don't let me die here. I don't wanna die.'"

When he awoke from a coma several weeks later, Jamal was in the ICU at Zuckerberg San Francisco General Hospital and Trauma Center (ZSFG). "That's when I saw Mike Texada for the first time," says Jamal, who is now 31. "He kept looking in on me without saying anything. I was so traumatized that I thought he might be trying to hurt me." Texada is hard to miss. He has the brawn of a football player, with broad, muscular shoulders, and the intensity of a man who has no time to waste. His beeper had gone off when Jamal hit the trauma bay, just as it does every time someone with a bullet or stab wound enters the ZSFG Emergency Department. As a case manager for the UCSF Wraparound Project, a hospital-based violence prevention program, Texada checks in on victims of violence who range in age from 10 to 35 and come from the most underserved parts of the city. He makes contact early so he can gauge whether patients are open to his help finding a way out of a life or associations that came dangerously close to killing them.

"I took my time introducing myself," recalls Texada of his early contact with Jamal. He waited until Jamal's father and uncle were in the room. "I could tell he was afraid of me, and it was understandable," Texada says. "Jamal didn't know who had shot him. Could have been me." Texada explained to Jamal and his relatives that Wraparound could connect them

with services that would cover some of the hospital bills that were already piling up and with a trauma-mental health specialist who could address Jamal's fears, which were just as evident as the stitches across his face.

Texada kept appearing at Jamal's bedside. "I had tubes and drugs in me and a flesh wound, so I couldn't really talk, but Mike did," says Jamal. "He kept telling me how strong I was. How it was a blessing that I was here. And he's been with me ever since, from that first day on, dissecting every situation and giving me some information about a little piece of everything."

Shutting the revolving door

The roots of the Wraparound Project go back to 1996, to a young doctor named Rochelle Dicker, MD, who was doing her surgical internship at San Francisco General Hospital. Dicker had developed a solid rapport with one of her patients, a 16-year-old shooting victim from Bayview Hunter's Point. "I got to know him quite well," recalls Dicker. "He told me he wasn't going to graduate from high school at 18. He thought there was a good chance that he wouldn't live past 25. He saw no way out, except for his friends protecting him."

Not yet 30 herself at the time, Dicker was struck by the contrast between her patient's life and her own, which was just blasting off. "My life bore no resemblance whatsoever to what this 16-year-old was talking about," she recalls. Shaken by fear, her patient wanted a way out of where his life was headed, but he just didn't see one. Dicker came to call these windows of opportunity "teachable moments" – times when, with the right intervention, these young adults, mostly men, might redirect their lives.

Wraparound case manager Mike Texada (left) has guided Jamal (right) throughout his recovery.



"I was trying really hard to give him hope, but I couldn't tell him where to get a good education or a job like the one I had at a bakery when I was 16. I didn't have any answers for him."

A few weeks later, her patient was back in the ER with another bullet wound. "It struck me then that violence is a chronic disease," Dicker remembers. That realization inspired her, some seven years later, to create the Wraparound Project as part of a Violence Prevention Fellowship. Wraparound seizes teachable moments to offer a comprehensive

"THE TEACHABLE MOMENT IS WHEN YOU TELL THEM, 'YES, YOU CAN GRADUATE, YOU CAN GET A JOB, YOU CAN GET OFF PROBATION, YOU CAN GET OFF PAROLE.'" – MIKE TEXADA

care plan that encompasses financial relief, housing, trauma recovery, education, and employment. The goal is to help people like her young patient not get trapped into a cycle of violence or retribution and work toward a new life.

What Dicker had witnessed happens with great frequency on a national level. The strongest risk factor for violent injury is a history of previous violent injury. In fact, for someone who has been a victim of violence, the chance of reinjury is as high as 45 percent and death from violent injury is twice as likely. Yet by the time Wraparound was just 10 years old, it had changed that grim statistic within the city of San Francisco. By 2008, the project had reduced injury recurrence from 16 percent during the five years before its inception to 4.5 percent during its first five years of operation. Today, Dicker focuses on developing hospital-based injury prevention programs modeled on Wraparound. With five colleagues – surgeons, emergency medicine physicians, and public health professionals – from around the country, she formed the National Network of Hospital-Based Violence Intervention Programs (NNHVIP). Together, they have now created 34 such programs nationwide.

Seizing the moment

The Wraparound Project is housed in a spartan space at ZSFG, with just enough room for its director, Catherine Juillard, MD, MPH; four case managers; and an injury prevention coordinator, Adaobi Nwabuo, MBBS, MPH. It's situated right behind the emergency room so that Mike Texada and the other case managers can readily appear at the bedsides of young victims of violent crime, to make sure no window of opportunity passes without someone there to reach through it, hold the patient's hand, listen hard, and guide them toward resources. The case managers work to make victims feel whole, safe, and independent enough to break out of the cycle of violence.

"To me, the teachable moment is really when the client has bare sight, when you have that real one-on-one conversation, without all the

negativity that's been around their lives, without all the stuff that they've been trying to deal with on their own," explains Texada. "It's when you tell them, 'Yes, you can graduate, you can get a job, you can get off probation, you can get off parole.'"

Texada speaks with the authority of authenticity. Born and raised in the projects in San Francisco's Western Addition neighborhood, Texada has a story of his own – one that he shares openly and that his clients are very familiar with. He was busted twice for hustling drugs and did time in a state penitentiary in Susanville, Calif. "I changed my path for the love of my children," says Texada. "I decided that I really didn't want to be part of the problem. I wanted to be part of the solution." For the past 12 years, he has led by example through the Wraparound Project and recently received the NNHVIP's Willis Young Award for his extraordinary efficacy.

Piece by piece

Even before Jamal was shot, his life wasn't easy. His mother died of a heart condition when he was 16 years old. He lived with his father and aunt in the Fillmore. His little brother had at one point been removed from the household by protective services while his father fought through some drug issues. "I grew up seeing a lot of people I know personally dying from gun violence in this city," says Jamal. "And a lot of those friends died at the General [ZSFG]."

So Texada seized the teachable moment that opened up for Jamal during his recovery from his own shooting. Jamal had to undergo reconstructive surgery to piece his face back together. The hospital bills were insurmountable. Texada connected him with Victims of Crime, a national victims' rights nonprofit, to help him pay for his care. But even now, seven years later, Jamal is still trying to earn enough money for dental implants. Standing next to him, you wouldn't know that a scalpel – much less a bullet – had ever touched his face. The work is seamless. "But I can feel it from the inside," Jamal says.

Putting Jamal's face back together was far easier for his surgeon than the task confronting the Wraparound team: making Jamal feel whole and safe. "Our clients need to address their mental health issues before they can work on their other needs," says Nwabuo, who manages Wraparound. "Even though mental health is very

Wraparound Services

In partnership with community-based organizations, the Wraparound Project provides the following services to invest in individuals and communities affected by violence:

- Crisis response services
- Vocational training
- Employment opportunities
- After-school programs
- Mental health services for victims and families
- Cognitive behavioral therapy
- General education degree (GED) resources
- Higher education
- Art workshops
- Assistance in obtaining driver's licenses, temporary disability benefits, and crime victim services

Violence as a National Disease

“The only way to stop violent injury is to reframe it as a disease and a crisis of public health,” insists Catherine Juillard, MD, MPH, Wraparound’s director through late 2018. The lives the project has saved in San Francisco prove her point: Violence can be addressed, treated, and prevented. Yet the scale of violence nationwide is gargantuan. Homicide is the number one killer of African American men and the number two killer of Hispanic men in this country. “Any time in public health when you see negatives that are not evenly distributed amongst populations, there are risk factors there that need to be identified and addressed,” says Juillard. “Study after study shows that the risk factors for violence are low socioeconomic status, poor educational attainment, and being exposed to violence at a young age.”

Rochelle Dicker, MD, Wraparound’s founder, and Juillard are both proponents of evolving medical education to address the social determinants of health. “I am constantly amazed by the challenges our clients face that people with higher socioeconomic circumstances do not: growing up in abject poverty; not having parents; being intermittently homeless; trying to stay in school but having no support; having relatives with chronic diseases who are constantly in and out of care and not able to really be a source of support for them,” says Juillard. “Diabetes, heart disease, cancer – all of these diseases happen disproportionately to the same communities that are affected by violence. It’s like a snowball.”

Guns are an obvious common denominator of violent injury, and Dicker and Juillard both support proposed laws that would reduce the incidence of gun violence – like background checks and fingerprint activation.

Juillard was on duty the day a woman snuck into YouTube’s headquarters in San Bruno, shot three people, then killed herself. Those three victims, who all survived, arrived in the Zuckerberg San Francisco General Hospital trauma bay.

“The press descended, as they always do when white people are getting killed,” Juillard says. “Yet yesterday we had five shooting victims here, not white.... It’s like a mass shooting playing out every day in some neighborhoods, just in slow motion. Yet that is somehow expected. Violence has been silently normalized by our culture in certain communities. Violence isn’t normal, not for anybody.”

stigmatized, we match about 75 percent of our clients with mental health services at UCSF’s Trauma Recovery Center. These therapists are very cognizant of the people they serve, and our clients respond very well,” she says. Indeed, Jamal was so traumatized by the shooting that, at first, he was afraid to leave his home. “At the beginning, I was afraid of cars, especially cars with tinted windows, afraid to get on buses, afraid to be around groups of people, afraid of walking, afraid of friends. I didn’t know who shot me. It could have been anybody,” says Jamal. Wraparound connected him with a psychiatrist and a trauma recovery specialist. He saw them for years.

Tyranny of trauma

Lynsey Clark, a clinical social worker at UCSF’s Trauma Recovery Center, works two days a week with Wraparound clients. She helps them come to terms with the trauma of the physical incident that landed them in the hospital as well as, for most of them, the trauma of living in communities infused with violence. The two are intermingled. “Being a victim of a violent crime really changes your perspective about life, your mortality, and your relationships,” she says. Her clients suffer from hypervigilance, avoidance, nightmares, and flashbacks – all hallmarks of post-traumatic stress disorder (PTSD). “If patients don’t get treatment for PTSD, their worlds get smaller and smaller,” Clark adds. “Avoidance can be especially undermining.” By being so fearful of leaving his house, Jamal couldn’t finish his degree or get a job. His life came to a standstill.

Although his former employer encouraged him to come back to work – even bringing balloons and get-well letters to the hospital – Jamal said no. The landscaping job would take him into parts of the city where he didn’t feel safe. If Jamal had been his family’s primary breadwinner, as many Wraparound clients are, the loss of his income would

THERE ARE NOW 34 HOSPITAL-BASED VIOLENCE PREVENTION PROGRAMS NATIONWIDE SIMILAR TO UCSF’S WRAPAROUND PROJECT

have been devastating, completely undermining the entire family’s economic standing. “If you can’t leave your house, you can’t hold down a job, and you can’t contribute to the family income,” says Clark. “If you were the primary breadwinner, your role has fundamentally changed within the family. That changes how you feel about yourself, about others, and the world.”

Clark helps Wraparound clients set new goals. “For some clients from communities of violence who have experienced multiple traumas, their goal might be to sleep through the night without a nightmare or ride the bus without having a panic attack,” says Clark. Jamal credits his therapist with teaching him how to cope. “I now know steps to take if I go into a panic attack. I can take time to gather my thoughts, get my consciousness together and make better, rational, safe choices in the moment,” he says.

Jamal is now able to ride the bus – yet like many other Wraparound clients, he spends hours taking indirect routes so he can circumvent dangerous neighborhoods. “The reality of it all is that if something you are afraid of is really out there,” says Jamal, “the coping part doesn’t matter.”

Closing the wound

Jamal has come a long way over the past seven years. He has tapped into every resource Wraparound offers. Texada helped him enroll in Five Keys Charter School so he can finally finish his GED. Jamal has used Wraparound’s Advocacy Center to get tutoring help along the way. Wraparound’s Job Readiness Training program helped him develop a resume and interviewing skills, which enabled him to land a job at a shelter for juveniles who have been removed from their families.

A Wraparound volunteer also taught Jamal how to paint. His first painting was a portrait of his mother. He has painted her image time and again, each time straying more freely from what she looked like and delving more into what she represents – a source of love, happiness, and, in her absence, pain. He paints a broad range of other subjects, too – from the Simpsons, to wild creatures of the night, to the galaxy. He has now produced dozens of paintings, his work has appeared in shows, and he successfully sells his art.

Today, Jamal considers himself an advocate for victims of violence. In this capacity, he is paying forward all he has learned from Texada. “Jamal has potential as a peer leader,” says Texada. “He is inspiring in intimate settings, when people need help identifying who they are and what they need.” The two work together in Texada’s Weapons in Minors’ Possession Program, which invites kids who have been busted for carrying guns to come to ZSFG. There, Texada and Jamal tell them cautionary tales of the path that weapons might lead them down.

Jamal speaks to these kids knowing exactly where they are coming from. They are just trying to survive a world that is falling down around them. “Some of these kids have brothers and sisters who were murdered, fathers and mothers on drugs. Some never even knew their parents and are growing up in a bad community witnessing a whole bunch of different things,” explains Jamal. “The brain can be sculpted any type of way. These situations in neighborhoods – what kids see – it affects how they interpret life and how they want to live it.” Acquiring a gun in such a scenario might make them feel safer. Jamal’s message is that owning a weapon never ends well.

“I tell them there’s always a way out. I tell them to pay attention in school, to graduate on time, to ignore the cool kids with the Jordans,” says Jamal. “Trying to get those shoes is a gateway to everything else that’s negative in the world – stealing, selling drugs. It’s hard for them to see the pros when there are so many cons in their world. This is my perspective on how we can help the world.”

Jamal now gets letters from kids telling him how he has righted their course. “Mike Texada put one on his wall,” says Jamal, beaming. It’s clear that Texada’s approval means everything to him. Yet it has to be earned, and Jamal is currently working furiously to win it back. He was recently busted on a weapon possession charge, so Texada suspended him from his advocacy role until he pulls himself back together. “I have a lot of love, but it is tough love,” says Texada. “I don’t have sympathy when you make mistakes that you know better than to make. I want him to man up and take responsibility.” But the “love” part is that Texada has gone to a couple of



court sessions with Jamal to advocate for him.

Having had setbacks of his own, Texada sees this as the rough terrain Jamal must get through to become an adult. There’s no easy way out of the cycle of violence. The pictures on Texada’s wall – a mosaic of faces – tell that story all too well. Some of those faces have the doughy look of middle school, others have the finer chisel of young men in their twenties. Nearly all are boys and men of color. Texada can swivel around in his desk chair and name each of them – where they are, what they are up to. “I still talk to this guy,” he says, pointing to a picture of fifth-graders around a craft table. “He’s in jail for attempted murder; his brother was murdered yesterday. This guy just got out for attempted murder,” he continues. “He’s got a job right now. Just had a new baby. And this young man just did a rap song that went viral. He’s going to start making some money.” All told, their stories trace the arc of Texada’s career, from his early work as a school site mentor, intervening with troubled kids for an antiviolence group called Brothers Against Guns, to his current position at Wraparound.

“Yeah, I had some of these guys in grammar school. Now I see them coming through the trauma bay,” says Texada, with a wince. He has spent seven years making sure Jamal’s story is a long and positive one.

“There have been times when I’ve strayed away from this program, times I might have started things that I didn’t finish,” says Jamal. “But I always come back. The door never closes.”

Surgeon Rochelle Dicker’s experience with a teenage gunshot victim during her UCSF internship sparked her idea for Wraparound.



UNCOVERING THE SECRETS AND SICKNESS BENEATH THE SWEET SURFACE

BY ANNE KAVANAGH

Walk into any grocery store, grab a few packaged products, and flip to the ingredients. You'll likely spot added sugars – lots of them – provided you can discern their dizzying array of names: sucrose, dextrose, barley malt, agave nectar, high-fructose corn syrup, treacle, to list just a few.

Why is our food saturated with all these sweeteners? When did they make their way into our yogurt, cereal, and oatmeal? How did they sneak into our salad dressing, soup, bread, lunch meat, pasta sauce, and pretzels?

And, most crucially, what forces are responsible for this deluge, which is making some of us very sick?

UCSF scientists are uncovering the answers to those questions. What they're finding is that the food and beverage industry pushes sugary products, while obfuscating the significant



On average, Americans eat about 17 teaspoons of added sugars every day. That adds up to a whopping 57 pounds a year.

health hazards of added sugars. UCSF researchers are scrutinizing this influence, scouring the research to better understand sugars' link to disease, and fighting biased science by exposing industry tactics and educating the public.

THE MORE WE EAT, THE SICKER WE GET

When Dean Schillinger, MD, was a resident at San Francisco General Hospital in the early 1990s, almost half his patients had HIV or AIDS. Today, he's chief of general internal medicine at the hospital, and a new crisis occupies him: Nearly half his patients have type 2 diabetes. Many grapple with its horrific toll, including blindness, kidney failure, amputations, heart attacks, and strokes.

"Our AIDS ward has become a diabetes ward," says Schillinger. "It happened in front of my eyes in basically one generation."

Startling statistics bear out Schillinger's experience: Since 1970, the incidence of diabetes has more than tripled (type 2 diabetes accounts for about 95 percent of that increase). In California alone, 11 percent of adults have diabetes and 46 percent are prediabetic. That adds up to over half the state's population. Another troubling fact: People of color and those at lower income levels are at higher risk of having type 2 diabetes and are getting it at younger and younger ages.

Nearly one in four teens has prediabetes, placing them at very high risk of acquiring full-blown diabetes within 10 years, in the prime of their lives. About one in two children of color born today will be diagnosed with type 2 diabetes during their lifetimes.



"We need the general public to become aware of what's going on" with industry influence, says Dean Schillinger (below).



It's not the only disease that's reared its ugly head in recent decades. Nonalcoholic fatty liver disease – a buildup of extra fat in liver cells, which can lead to cirrhosis, or scarring of liver tissue – wasn't even a known diagnostic entity 30 years ago. Now almost one-third of U.S. adults have it. The disease is on track to become the leading cause of liver transplantation within five years. And doctors are treating the first generation of *kids* with fatty livers.

The dramatic spike in these diseases isn't caused by genetic changes, a common misbelief, says Schillinger. "Something in the environment has changed."

That "something" includes many societal shifts – such as sedentary lifestyles and larger portion sizes – as well as greatly increased consumption of added sugars, say Schillinger and others.

Americans eat far more packaged foods and consume more sugary beverages than we did 50 years ago. And sweeteners are almost impossible to escape: They're in three-fourths of packaged products. Liquid sugar, in the form of sodas, energy drinks, and sports drinks, represents 36 percent of the added sugar we consume. On average, Americans eat about 17 teaspoons of added sugars every day – substantially more than the U.S. Dietary Guidelines' recommended maximum of 12 teaspoons on a 2,000-calorie diet. That adds up to a whopping 57 pounds a year.

"Our food system is completely out of whack," says Laura Schmidt, PhD, MSW, MPH, a professor of health policy and the lead investigator of UCSF's SugarScience initiative.

A growing body of scientific evidence now links long-term overconsumption of added sugars to diabetes, cavities, liver disease, and heart disease. Much of this evidence focuses on a cluster of metabolic issues, known collectively as metabolic syndrome (MetS), that raises people's risk of developing chronic diseases. These issues include insulin resistance, elevated blood sugar, high blood fats (triglycerides), high cholesterol, high blood pressure, and a condition known as "sugar belly."

One of the main culprits in MetS is fructose. Fructose is found naturally in fruits and honey, but in processed foods and sodas it's been extracted from corn, beets, or sugarcane, stripped of fiber and nutrients, and concentrated. Nearly all added sugars, even healthy-sounding ones like organic cane sugar, contain significant fructose. Table sugar, for example, is 50 percent fructose. The most common type of high-fructose corn syrup, a concentrated, liquid form of added sugar, is about 55 percent fructose.

The problem with fructose is that the body can turn only so much of it into energy; the liver transforms the rest into fat globules called triglycerides, which in excess can wreak havoc. The liver releases some of these into the bloodstream, causing "sugar belly" (an especially dangerous form of body fat) and raising cholesterol levels (which are linked to heart disease).

PHOTO: MARCO OLIVIERI LE BLANC

Even worse, the triglycerides that stay in the liver affect insulin's ability to regulate blood sugar, a condition known as insulin resistance. This causes more fructose to be turned into fat and accelerates the amount of fat the liver releases into the blood. It's a vicious cycle – one too many Americans are trapped in.

With almost half of Californians and millions of others nationwide at risk of developing full-blown diabetes, “we are sitting on a ticking time bomb,” says Schmidt.

DOCUMENTS REVEAL SCIENTIFIC SHENANIGANS

In 2007, Cristin Kearns, DDS, MBA, began an unlikely journey that would shed light on some of the forces that helped push us to this brink. Her foray began years before she became an assistant professor at UCSF, at a dental conference on the connection between gum disease and diabetes. One of the keynote speakers gave his seal of approval to Lipton Brisk, a sugar-laden tea. Aghast, Kearns chased him down and asked how he could possibly call sweetened tea healthy. “There is no evidence linking sugar to chronic disease,” he calmly replied.

“I was speechless,” Kearns recalls. “I literally had no words.”

After all, she had seen how sugary drinks damaged her patients' oral health. Some had cavities in every tooth, and she knew tooth decay was the leading chronic disease afflicting kids.

Another speaker at the conference, this one from the federal government's National Diabetes Education Program, shared a dietary advice pamphlet that said nothing about sugar intake. “I found that strange,” says Kearns. She had worked in an inner city clinic where many patients had diabetes, and it was clear to her that excess sugar played a role in their disease.

What was going on? Kearns couldn't let go of that question, so she went home and started researching sugar. Driven by a nagging hunch, she focused on the players behind the disconnect between her experience and what she heard from “experts.” Up popped the website of the Sugar Association, a trade group that dates back to 1943; its members include Domino Sugar, Imperial Sugar, and other sugar producers.

The more Kearns unearthed about the Sugar Association, the more convinced she became that they were influencing science and federal policies. She quit her job to dig into archives all across the country. One day, she hit the mother lode: 1,500 internal Sugar Association documents related to a public relations campaign the industry had launched in 1976. The documents clearly showed the industry's plan to influence the Food and Drug Administration's regulatory

**“OUR AIDS WARD HAS
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review of the safety of sugar. “I couldn't believe I'd found it,” she says.

Kearns came to UCSF as a postdoctoral fellow in 2013 to learn how to analyze industry tactics, drawn by the faculty's expertise combating the tobacco industry. In the 1990s, UCSF's analysis of thousands of tobacco industry documents showed that tobacco companies had known about the grave dangers of smoking for decades, but they withheld that information from the public to protect their profits.

The fruits of her labor revealed the sugar industry's decades-long strategy to downplay sweeteners' potentially harmful health effects. She found strong evidence that the industry had manipulated science to protect its commercial interests, influence regulations, and shape public opinion. (The industry has disputed this assessment through public statements by the Sugar Association.)

One of her studies, published in *JAMA Internal Medicine*, showed that the Sugar Research Foundation, which later became the Sugar Association, recognized as early as 1954 that if Americans adopted low-fat diets, then per-capita consumption of sucrose would increase by more than one-third.

By the mid-1960s, however, researchers had begun wondering whether sugar might be related to heart disease. The Sugar Research Foundation paid three Harvard scientists today's equivalent of \$50,000 to review the existing research on sugar, fat, and heart disease. Their analysis, published in the prestigious *New England Journal of Medicine (NEJM)*, minimized the link between sugar and heart health and promoted fat as the culprit instead.

“It was clearly a biased evaluation,” says Kearns, who spent a year analyzing the communications between the

industry and the researchers, as well as the studies included in the review. “The literature review helped shape not only public opinion on what causes heart problems but also the scientific community’s view of how to evaluate dietary risk factors for heart disease,” she says.

These tactics contributed to the low-fat craze, which began in the early 1970s and paralleled a rise in obesity, according to Kearns and Schmidt. Many health experts encouraged Americans to reduce their fat intake, which led people to eat foods low in fat but loaded with sugar (think SnackWell’s cookies). The trend is an example of “how industry has deeply penetrated science in order to distort the facts about what’s good for our health,” says Schmidt, a co-author of the *JAMA* paper.

Another of Kearns’s studies, published in *PLOS Biology*, showed that the industry also withheld critical scientific evidence. In 1968, the Sugar Research Foundation funded a research project on animals to illuminate the connection between sugar and heart health. Early results uncovered a potential link between sucrose and bladder cancer. Within weeks of obtaining conclusive evidence that sucrose elevates blood triglycerides by interacting with gut bacteria, the foundation ended the study. The results were never published. At the time, the FDA was deciding whether to take a hard stance on high-sugar foods. Kearns says if the results had been made public, sugar might have been more heavily scrutinized.

With thousands of documents still to analyze, and more archives being identified, she believes she has just scratched



“Our food system is completely out of whack,” says health policy expert Laura Schmidt (right), who collaborates with sugar industry investigator Cristin Kearns (left).

the surface of the industry’s influence. “It’s vast,” she says. “I could be doing this for years.”

Diabetes expert Schillinger has also been probing biases in sugar science. In a report in the *Annals of Internal Medicine*, co-authored with Kearns, he reviewed the 60 studies between 2001 and 2016 that looked at whether sugary drinks contribute to obesity or diabetes. Of the 26 studies that found no link, all were funded by the sugar-sweetened-beverage industry or conducted by people with financial ties to the industry. Of the 34 studies that found a link, just one was funded by the beverage industry; the rest were independently funded.

“It was by far the strongest relationship ... I’ve observed between conflicts of interest and science,” Schillinger says.

STOP BLAMING YOURSELF

Since sugar-related chronic diseases are largely preventable with changes in diet and physical activity, there’s a tendency to point fingers at people for making bad choices and being lazy. Soda companies add to the cacophony by claiming their products can be enjoyed as part of a healthy lifestyle.

Such ideas are bunk, say sugar scientists.

“We need to stop blaming individuals for getting sick and start changing our crazy food environment,” says Schmidt. “It puts an incredible burden on individuals. People’s choices are very limited when 74 percent of our food has added sugar.” And that burden falls most heavily on those without the time and money to purchase and prepare healthy foods.

Scientists and policymakers can change the environment by pursuing the same public health prevention strategies used to combat Big Tobacco, Schmidt says.

“It’s easy to forget that back in the ’50s and ’60s, smoking was the norm,” she explains. People smoked

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on airplanes, at work, in restaurants, even in hospitals. “You could buy cigarettes in our medical center vending machines,” she says. “Public health officials changed the environment. They made it unpopular to smoke.” They did so by amassing evidence of tobacco’s dangers, warning people of its harms, advocating for taxation, pushing to get cigarettes moved behind counters, and calling for smoking to be banned from bars and public buildings, among other approaches. Eventually, the death rate for lung cancer plummeted.

“We’re in the beginning stages of that kind of public health battle around sugar,” Schmidt says. UCSF has already started implementing many strategies, including these:

Provide evidence-based information to lawmakers and the public.

UCSF’s SugarScience.ucsf.edu website highlights the evidence about sugar and its impact on health. The site reflects an exhaustive review of more than 8,000 scientific papers published to date. Studies are rigorously reviewed, including for author bias and conflicts of interest.

In addition, the UCSF Industry Documents Library – which houses tobacco industry documents – and the UCSF Philip R. Lee Institute for Health Policy Studies launched the first-ever food industry document archive in November 2018. It includes thousands of previously secret documents by food industry executives, including Kearns’ stash, illuminating how the industry manipulates public health. It’s open to journalists, academics, and the public.

Tax products that make us sick.

Schmidt is working on soda tax initiatives with policymakers in the Bay Area and around the world, from India to Africa to Mexico. “Taxes trigger what I call a virtuous cycle of policymaking,” she says. Taxes gently discourage consumers from buying harmful products, while also generating funds that governments can pour into prevention – such as better screening for diabetes, construction of water refilling stations in low-income communities, and promulgation of public health messages.

The beverage industry, however, argues that such taxes make it harder for low-income individuals to buy groceries and unfairly single out soda. But this isn’t the case if the tax proceeds are returned to low-income communities through programs promoting healthy food and clean water access, Schmidt counters. The industry has spent millions of dollars around the country over the past decade to defeat soda tax initiatives. In June 2018, the California legislature passed a bill championed by the soda industry banning California cities and counties from passing new taxes on sugary beverages for 12 years. UCSF’s researchers say this significantly undermines the cities and counties from preventing diet-related chronic diseases through such taxation.

HOW TO CUT YOUR SUGAR

1. CUT SUGARY DRINKS. Wean yourself slowly if going cold turkey is too much to bear.

2. KEEP TEMPTATIONS OUT OF REACH. Clean up your pantry and fridge and skip the supermarket’s junk aisles entirely.

3. LIMIT YOUR KIDS’ EXPOSURE. But don’t go overboard, or the “forbidden fruit” will be even more enticing.

4. BE WARY OF BOXED, BAGGED, AND CANNED FOODS. And remember: Organic, “natural,” and other healthy-sounding products often still pack hidden sugars.

5. TAP YOUR COMMUNITY. Could your workplace, your gym, or your kid’s school take a stand for healthier choices?

“That was a really bad week,” says Schmidt. “These companies have us totally outgunned. It’s like David versus Goliath.” Such struggles are why it’s essential for scientists to get evidence into the hands of policymakers and the public, she says.

Warn people of the harm.

Schmidt, Schillinger, and others at UCSF are trying to issue warnings, but the soda industry is thwarting these efforts, too. The researchers worked with local legislators to help pass, in 2015, the world’s first ordinance requiring billboards advertising sugar-sweetened beverages to include a warning notice. “This was huge,” says Schillinger. “A brilliant landmark for public health.”

But the beverage industry challenged the ordinance, and an appeals court blocked it, saying it unfairly targeted one group of products. In January 2018, the appeals court said it would rehear the case.

WAKE UP TO THE INFLUENCE

“We need the general public to become aware of what’s going on,” says Schillinger, who was a paid expert for the City of San Francisco’s defense against the industry’s lawsuit to block the billboard ordinance. That experience, along with his research and boots-on-the-ground care of patients, has convinced him the sugar struggle is a societal problem that needs many more stakeholders. “If this is just a medical issue versus industry, we will lose,” he says.

To that end, Schillinger co-created a social media campaign encouraging youths of color to voice their outrage in first-person, spoken-word pieces that reframe diabetes as a social and environmental problem, not just a medical one. Called “The Bigger Picture,” the campaign has garnered nearly 2 million views and won numerous public health and film/media awards. Many health departments have adopted it for their own public messaging.

Schmidt points to other encouraging trends – soda taxes have been implemented in 33 countries, for example – but says we still have a long way to go to prevent the looming tsunami of sugar-fueled diseases.

“These industries know sugar sells, they know it tastes good, they know people want it. They’re not going to stop doing what they do,” she says.

But with science on their side, neither will UCSF’s researchers. They’ll continue to seek a sweet ending to the reign of added sugar.

LEARN MORE

SugarScience.ucsf.edu (an authoritative source of scientific evidence about sugar)

industrydocumentslibrary.ucsf.edu (an archive of food industry documents)

thebiggerpictureproject.org (a diabetes education campaign)

THE FIGHTER

Who Plans to
Survive and Soar

Jazz Hardict is a born performer, one with big plans for her future. The vibrant 9-year-old suffers from sickle cell disease, a genetic blood disorder that causes severe pain and can cut lives short.

Jazz's care team at UCSF Benioff Children's Hospital Oakland is determined to give her a shot at her dreams. Meanwhile, UCSF scientists are sprinting to find a cure within her lifetime.

Defeating sickle cell disease is just one of our many audacious goals. Through **UCSF: The Campaign**, our researchers, care providers, and educators are taking on the hardest problems in human health, and in the campaign's first year, almost 45,000 friends and supporters have joined us in this mission.

[CAMPAIGN.UCSF.EDU](https://campaign.ucsf.edu)



Watch Jazz's story:
bit.ly/ucsf-jazz





Enjoying a moment together at Alumni Weekend 2018: (from left) Leon Davis, DDS '85; Bobby Kennedy, DDS '86; Denise Alexander, DDS '86; and Larry Guittard, DDS '86.

You are invited...

Alumni Weekend 2019 is Friday and Saturday, April 12-13, at the Hyatt Regency San Francisco. Come for tours, great speakers, receptions, reunion programming, and much more. Don't miss next spring's big fling!

Learn more about it at
alumni.ucsf.edu/aw

Eric Topol, MD, Resident Alumnus

Birthplace: Queens, New York

Now: La Jolla, Calif.

Position: Executive vice president and professor of molecular medicine, Scripps Research Institute; founder and director, Scripps Research Translational Institute

Hobbies: Hiking, kayaking, golf, spending time with his family

Cardiologist **Eric Topol** is turning the medical establishment on its ear with his vision of a democratized health care system driven by patients and empowered by “medicalized” smartphones. He heads the consumer-facing component of the National Institutes of Health’s Precision Medicine Initiative, which aims to harness and analyze a treasure trove of medical data from one million citizen-science participants nationwide.

What could the future of medicine look like?

There has never been such a dynamic and transformative time. We can sequence an individual genome and find the medical essence of each human being, but it’s not just about the genes. We also now have ingenious apps and sensors to record your heart rhythm, blood pressure, and glucose levels. We have artificial intelligence algorithms that can process the multiple layers of our data, including our genome and our environment. These tools are going to make us more efficient and more productive. They will put the patient more in charge of his or her own health, and they will give doctors more time to invest in our patient relationships and in our caring.



PHOTO: MICHAEL BALDERAS

“We have artificial intelligence algorithms that can process the multiple layers of our data, including our genome and our environment. These tools are going to make us more efficient and more productive.

– Eric Topol, MD, Resident Alumnus

How did you first get interested in genetics?

I was enamored with the idea that we could manipulate aspects of our genes. My 1975 college thesis was called “Prospects for Genetic Therapy in Man,” but I didn’t realize it would take us 40 years to get there. Gene therapy is very complicated. We rushed into it in the ’90s, and the early death of a teenager as part of a clinical trial for a rare metabolic disease set back the field research and trials almost 15 years. Now we’re on a solid footing; with newer techniques like CRISPR, we can approach diseases – sickle cell, thalassemia, hemophilia – that were unapproachable before.

What will it take to reform health care in the U.S.?

We could see a consumer revolution – a “Health Spring” – where people start rallying for change. More likely, it will come from the largest companies, which have hundreds of thousands of employees (and their families) and billions in yearly expenditures for their health coverage. We’re learning from countries that use single-payer systems, artificial intelligence, and other tools to create greater efficiencies. My guess is that we will see movement in this country, because right now things are moving in the wrong direction in terms of access and expense. And the burnout, depression, and suicide rates among physicians are staggering.

What’s the coolest part of the Precision Medicine Initiative?

We’re doing well getting people to participate. The tricky part is getting enough underrepresented minorities involved so that we have a diverse pool of one million individuals. The output will be enormous, and we’re going to learn so much. Some of the quick things we’ll learn: What is normal blood pressure? What is normal glucose after eating? We have no idea, because we measure these things in a doctor’s office, which is the most contrived setting. Look what the landmark Framingham Heart Study, a longitudinal study of cardiovascular disease in 5,209 people, has taught us about heart disease – more than any other study in the field. Now we’ll learn so much about health and virtually all medical conditions.

What has been the one constant in your career?

I’ve only had three jobs in my life – at the University of Michigan, then Cleveland Clinic, and now Scripps – and I’ve never had to give up seeing my cardiology patients. I love that, and I have at least 30 minutes with every patient I see. Time, to me, is vital. You can’t be rushing and interrupting people; you have to let them tell their story.

SCHOOL OF NURSING

DorAnne Donesky, MS '90, PhD '03

Birthplace: Lacombe, Alberta, Canada

Now: Vallejo, Calif.

Position: Professor, UCSF School of Nursing; Director, Interprofessional Palliative Care Education

Hobbies: Gardening, hiking, preparing and drinking tea, reading, travel

DorAnne Donesky knew she was destined to be a nurse. She has carved out a specialized career caring for people with life-threatening respiratory illnesses, helping them manage the daily challenge of simply taking a breath so they can enjoy life as much as possible.

How did you discover your calling as a nurse?

My mother reminded me recently that when I was 4, I used to line up all my dolls and

animals with bandages and a blackboard in front. I couldn't decide whether to be a nurse or a teacher. Nurse? Teacher? Then one day, Mom tells me, my face lit up and I knew I would be a teacher of nurses.

What's your favorite thing about teaching?

We offer an interprofessional palliative care course once a month where everyone is learning together – chaplains, physicians, nurses, social workers – and we co-teach the entire time. It's exhausting and exhilarating, the most inspiring teaching I've ever done. The synergy of our different perspectives is what interprofessional work is all about.

How did you develop your deep connection with respiratory illness?

I have the utmost compassion for people living with chronic

lung diseases. Breathlessness is frightening. They have to manage very distressing symptoms, using inhalers and other equipment, and they need a lot of education and daily support. Most people who are breathless feel so stigmatized; I try to offer some extra love and kindness.

How do you approach your patients who are near the end of life?

Regardless of where my patients are in their life trajectory, I try to find out what's important to them and how I can support them to live the life they want, within the context of their health or illness. That is what nurses do, from perinatal to palliative care. I'm very proud of being a nurse.



Mark Kirkland joined the UCSF faculty the day after he graduated in 1983. Today, as associate dean, he works steadfastly behind the scenes on everything from student support and patient safety to clinical facilities – to ensure that the school meets the highest standards of excellence.

With all your administrative duties, do you still find time to teach?

I teach one half-day a week and really enjoy working with our learners. We want to teach them that there's more to dentistry than working on a tooth. Each person is unique, and we have to treat the whole person.

Tell us about the Commission on Dental Accreditation.

It's the accrediting agency for dental education programs, and it reviews all accredited schools every seven years to ensure they're meeting the

established standards. I'm one of a number of individuals working to prepare for next year's site visit. I'm glad we don't have to do this every three years, like the hospitals, but it's an important process. It forces you to look with a critical eye at what you're doing, what your goals are, and whether you're meeting them.

What changes have you seen in your 35-year career?

One of the big improvements has been infection control. When I was a student, we weren't required to wear gloves and masks. I remember the pushback: People said they couldn't do dental procedures while wearing gloves or that their patients couldn't hear them when they were wearing masks. It took a long time to get everyone to comply.

What is your favorite part of the week?

Working with my patients is very enjoyable. Some of my patients have been with me for many years, and now I'm also treating their adult children. You get an opportunity to know them. They put their trust in you, and that's a big responsibility – and a privilege.

SCHOOL OF DENTISTRY

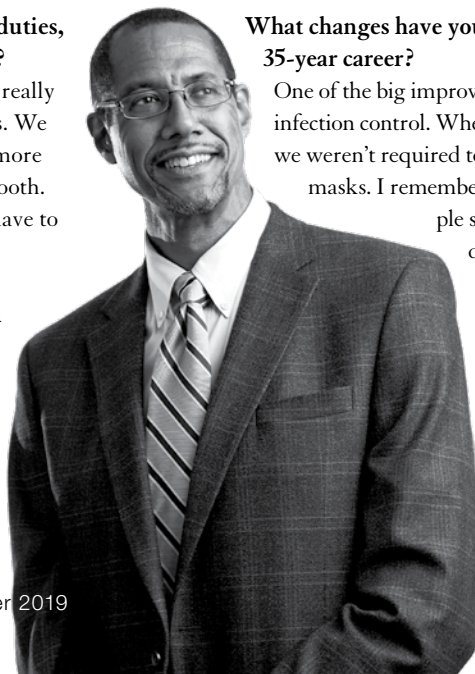
Mark Kirkland, DDS '83, Postgraduate Certificate in Advanced Education in General Dentistry '95

Birthplace: Sacramento, Calif.

Now: Pacifica, Calif.

Position: Professor and associate dean for clinical affairs, UCSF School of Dentistry

Hobbies: Working out, hiking, watching movies, listening to live jazz



PHOTOS: ELENA ZHUKOVA, STEVE BABULJAK

GRADUATE DIVISION

Sandra Waugh Ruggles, PhD '02 (Biophysics)

Birthplace: Los Altos, Calif.

Now: Sunnyvale, Calif.

Position: Faculty fellows mentor, Stanford Byers Center for Biodesign

Hobbies: Skiing, running, spending time with family

Sandy Ruggles has yet to find the one word that describes her work: She is an innovation chaser, an idea generator, and an impact amplifier who is helping small startups bring transformative medical technologies to market.

What were your early career influences?

I come from a family of innovators, including my grandfather, who started a chemical company after World War II. My father is an engineer, and my mom is a nurse. I've always been interested in the intersection of health

care and innovation, and I wanted to make an impact – not just one patient at a time, but on a larger scale.

Tell us about the company you started based on your biophysics PhD.

The company is Catalyst Biosciences, and I co-founded it with my thesis advisor, Charles Craik, and two colleagues. My role was scientific – designing proteases, the enzymes that break down proteins. Proteases are like those little craft scissors with different teeth patterns, and we changed those patterns to target different diseases. We started with a protease involved in clotting blood – factor VII – and engineered it to make it faster and better than the natural version.

Why did you move on?

I found the work hard because biotech development timelines are so long. I left Catalyst nine years ago,

and the lead product is still in clinical testing. At this point, I've switched from biotech to medtech, focusing on marketing strategy, clinical strategy, and business planning. I'm often the only marketing or commercial person on a team of mostly medical engineers.

What do you love about your work?

The best part of my day is when I get together with other really bright clinicians and engineers, and we just start brainstorming on thorny problems. That to me is a ton of fun.



In 2013, **Maria Lopez** launched Mission Wellness, a specialty pharmacy in San Francisco's Mission District, where she advocates for underserved Latino and African-American patients.

What is a specialty pharmacy?

A specialty pharmacy focuses on high-cost meds for complicated diseases like diabetes, HIV, and hepatitis C. These drugs are difficult to access and require special handling. Specialty pharmacists have additional training, and patients have to meet certain criteria. At our company, we provide testing, dispensing, packaging, delivery, and clinical support, and we have to file reports to show that our patients are complying with and benefiting from treatment. A UCSF study



shows that patients who get HIV medications through HIV-focused pharmacies have higher adherence than patients treated in other settings.

Tell us about your PrEP program.

We are the first California pharmacy to have pharmacists initiate PrEP, pre-exposure prophylaxis for HIV. It's a once-daily pill with more than 90-percent efficacy in preventing HIV infection. Mostly, PrEP has been studied in gay white men, but our goal is to increase access for Latinos and African Americans, who are disproportionately affected by HIV. We've tested several hundred patients and now have a number in treatment.

What inspired you to become a pharmacist?

I never thought I would be a pharmacist or a businesswoman. My mother's family has been in

California many generations, and my father was an immigrant farmworker. Education was not a priority, and I went to college against my parents' wishes. But right after I graduated from UCSF, I got the call that my father was dying. In the hospital, he was telling everyone, "My daughter is a doctor." He was so proud.

What's the best part of your job?

It's rewarding to see my employees and patients grow and reach their goals. Our care is very individualized, and our patients and providers really appreciate it. That's very gratifying.

SCHOOL OF PHARMACY

Maria Lopez, PharmD '01

Birthplace: El Centro, Calif.

Now: San Francisco, Calif.

Position: President and founder, Mission Wellness Pharmacy

Hobbies: Cooking, family trips to the mountains, skiing, biking



“My parents came here with nothing,” says Jessie Mai during a video shoot in Oakland, Calif., where she grew up. Inspired to transcend her own humble roots, she chose to study medicine at UCSF to combat health disparities and “to ensure that communities like mine have representation in health care.”



Watch Mai's story at bit.ly/ucsf-mai

UCSF

The
Campaign



PHOTO: SAROYAN HUMPHREY

YOUR INVESTMENT HER BREAKTHROUGHS

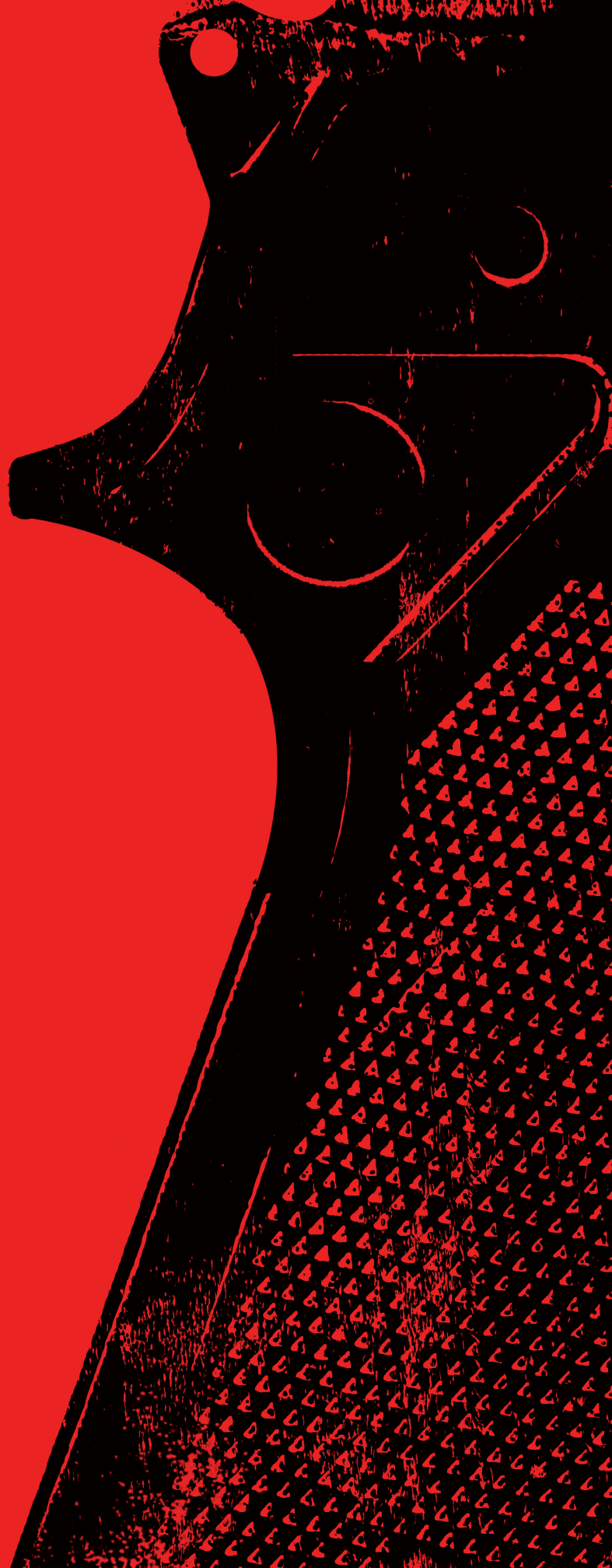
Teresa Monkkonen, PhD, is investigating whether certain types of chemotherapy drugs may inadvertently bolster some cancers even as they shrink the tumors that they target. Her work yields important insights into what's called "the tumor microenvironment," which is key to understanding how tumors grow in different individuals. Postdoctoral scholars like Monkkonen are critical to UCSF's research enterprise, and investing in their careers moves science forward.

"Professional conferences are invaluable for a postdoc like me. They help me think big and see my data in a new way. They can catalyze my next awesome experiment."

Visit makeagift.ucsf.edu/postdocs today to send scholars like Teresa Monkkonen to professional conferences that spark their breakthroughs – and have your gift **doubled** by a generous match from Larry and Irma Berkelhammer. Or visit makeagift.ucsf.edu/magazine to support another UCSF program.

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