UCSF

MAGAZINE

Summer 2018

Drug Odyssey

The epic journey to better medicines

UCSF MAGAZINE
SUMMER 2018

FEATURES

DEPARTMENTS

PEACE OF MIND
For kids with sensory processing disorder and their parents, life can be a struggle. But new research and treatments are helping them find calm.
See story on page 28.

COVER ILLUSTRATION: BRIAN STAUFFER; THIS SPREAD: GABRIELA HASBUN

In this first year of UCSF: The Campaign, I have often embraced bold language to describe the character of our community: the mavericks, the unorthodox, the revolutionaries, and so on.

One might wonder, why such a strong focus on breaking the mold?

Often, the conventional path is a journey of small steps forward. Such work is incredibly important. But at UC San Francisco, we seek to solve the most difficult problems in human health and biology. We believe in big leaps, and those often require new methods and ideas.

This issue is brimming with unorthodox approaches. Our cover feature explores how scientists in the UCSF School of Pharmacy are questioning the conventions of drug development to create better, faster, smarter, and more accessible treatments. Another feature dives into the marvelously innovative cellular therapy technologies developed by synthetic biologist Wendell Lim, and how the spectacular rise and acquisition of his biotech startup promises to speed his discoveries to patients. You will also read about neuroscientist Elysa Marco, who defied conventional approaches to a troubling condition known as sensory processing disorder, opening new pathways for care. And finally, public health researcher Dan Ciccarone shares his unusually intimate journey into the heart of America's opioid crisis – and his ambition to apply insights from this work toward ending the epidemic.

Wendell Lim, PhD, has pioneered cell therapies and cell engineering (see page 14).

UCSF is powered by people who are not just willing but *driven* to think outside the box. Our scientists, care providers, students and alumni, partners and donors: In the best sense of the word, we are truly a community of *radical* thinkers.

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

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PHOTO: STEVE BABULJAK

Nursing the Nation

Research shows that people of color represent only 10 percent of the health care workforce, while in just three decades, racial and ethnic minority groups in the U.S. will grow to become half of the population. UCSF's School of Nursing is tackling this inequity through several career-focused programs. The Pipeline to Health Careers project trains high school students from underserved communities to be patient actors, gaining confidence and exposure to health careers, while learning a marketable skill. They also get to practice their own clinical skills.

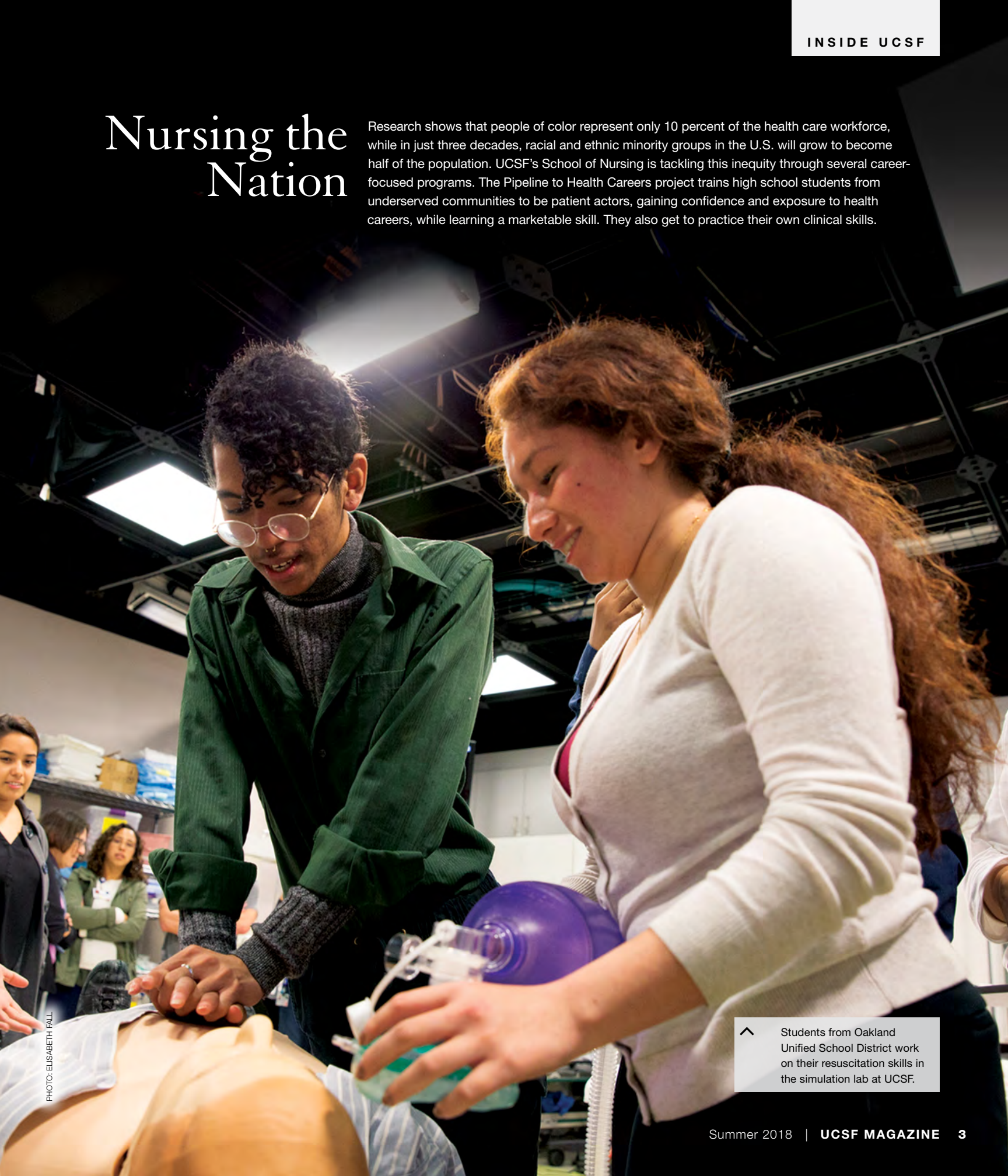


PHOTO: ELISABETH FALL

Students from Oakland Unified School District work on their resuscitation skills in the simulation lab at UCSF.

Staying Safe in the Sun

Sarah Arron, MD, PhD, resident alumna, director of the High Risk Skin Cancer Program at UCSF

Skin cancer is the number-one cancer diagnosis in the United States – it's more common than breast, prostate, and lung cancers combined. Skin cancers can be divided into two types – nonmelanoma (basal and squamous cell carcinomas) and melanoma, with melanoma being the least common but most life-threatening. Each year, some 90,000 people are diagnosed with melanoma. Sarah Arron, MD, PhD, shares her thoughts on skin cancer prevention and helps separate the facts from the hype.

Which SPF?
The sun protection factor (SPF) number indicates the time it will take for UVB rays to redden your skin. I tell my patients to choose SPF 30 or higher because most people do not apply sunscreen as directed.

SPF moisturizer?
These are a great idea! It's important that you like wearing the sunscreen enough to make it a part of your daily routine.

Eyes and lips?
Wear lip balm with SPF 15 and sunglasses with UV blockers in the lenses.

If being in the sun makes me happy, why should I protect myself from it?
Sun exposure can boost mood, and that makes sunshine addictive for some people. We like to rationalize that addiction by saying it must be healthy if it makes us feel or look good. But it's not. There is no such thing as a healthy tan, even though the tanning bed industry promotes its products that way. Until we dismiss the idea of a "healthy" tan, we'll continue to see an epidemic of skin cancer in this country.

Are there other ways to prevent skin cancers?
Seek the shade and avoid outdoor activities during the peak sun hours of 10 a.m. to 2 p.m. Sports enthusiasts can go out in the early morning, take a break, and go out again later in the afternoon. You can also buy UV protective clothing, including hats (in many styles), swim tights, swim shirts, sleeves for tennis players, and more.

What about my vitamin D levels?
It's true that one of the ways our skin makes vitamin D is through UV radiation. But there are many other ways to get vitamin D, such as leafy greens, fortified milk, and supplements. Moreover, it's rare that individuals are so scrupulous about avoiding sun exposure that it causes vitamin D deficiency.

WHAT DOES BROAD-SPECTRUM MEAN?

It means the sunscreen provides protection from both types of damaging ultraviolet (UV) radiation – UVA and UVB. Both contribute to skin aging and skin cancers. UVB is the dominant sunburn and suntanning ray, whether the ultraviolet rays come from the sun or a tanning salon, while UVA penetrates deeper into the skin, causing premature aging and wrinkling. The SPF number measures only UVB protection, so you need to make sure your sunscreen specifies UVA protection as well.

CHEMICAL VS. MINERAL?

Each has its pros and cons. Mineral sunscreens contain titanium and zinc oxide. People with sensitive skin may have less reaction to a mineral sunscreen. Some of my patients prefer minerals due to concern about chemical safety and a preference for a natural approach. The downside is that these may feel thicker and heavier and can leave a ghost-like sheen on the face. Chemical sunscreens include avobenzone and oxybenzone in their ingredients and are usually formulated to feel lighter and appear more elegant. Neither is more protective than the other.

DO PEOPLE WITH DARK SKIN NEED TO WEAR SUNSCREEN?

Yes. When the sun affects our skin, there are two levels of damage. One is immediate, which we recognize as sunburn and which mostly affects lighter-skinned individuals. Patients with darker skin who don't get sunburned may think their skin is protected, but there's a second kind of damage that leads to loss of elasticity and premature aging of skin, as well as DNA mutations in the cells that may ultimately cause skin cancer.

WHAT ARE THE WARNING SIGNS OF SKIN CANCER?

In general, with skin cancer we'll see a persistent lesion that is growing and changing in shape and appearance and that bleeds without ever healing. It's very important that people get to know their own skin and their own spots, so that when new things appear they can point them out to their primary care doctor or dermatologist. I recommend a head-to-toe screening with a dermatologist to establish a baseline for the future.

WHICH SKIN-PROTECTION WEBSITES ARE TRUSTWORTHY?

For our organ transplant recipients (who have a 60- to 100-fold higher risk of skin cancer), we produced a downloadable booklet – and the information in it is relevant to all patients: **skincancer.ucsf.edu**.

SUNSCREEN PHOTO: ZERBOR

After a Stroke, **Quick Action Matters**

In treating a stroke, time is a patient's most precious commodity. Brain damage occurs quickly: Every minute that a major blood vessel in the brain is blocked, 2 million neurons can die. A 15-minute delay in care can cost a patient a whole year of functional life – that is, the ability to walk, talk, drive, and otherwise live independently.

PHOTO: BRYAN MELTZ

Debbie Yi Madhok, MD, is improving the odds for stroke patients.

Debbie Yi Madhok, MD, an assistant professor of emergency medicine at UCSF and an attending physician at Zuckerberg San Francisco General Hospital (ZSFG), is trying to improve the odds for stroke patients. She designed a rapid-response protocol for ischemic strokes – strokes caused by blood clots in the brain – to reduce the amount of time between the moment patients arrive at the hospital and the moment they receive medicine or are rolled into surgery.

ZSFG's previous process – transferring incoming patients to a bed, evaluating them, calling for a neurology consultation, waiting for the neurologist's assessment, taking patients for a CT scan, then returning them to their bed to receive medication while surgical options were weighed – could result in an hour or more passing before treatment was administered. Under the new rapid-response protocol, suspected stroke patients are evaluated immediately upon arrival. If signs of a stroke are present, patients are taken right away for a CT scan. If the scan reveals a clot, a medication called tPA is administered to break it up. If necessary, patients are then taken into surgery to remove the clot.

Under Madhok's protocol, the hospital has reduced "door-to-needle" time from an average of about 45 minutes to less than 20 minutes – potentially, the difference between severe disability and near-complete recovery. Madhok is currently in the process of getting the protocol implemented at UCSF Medical Center, too.

"Now everyone is more in tune to when stroke victims are coming in and paying close attention to whether it's the real thing and whether we need to intervene," says Christopher Colwell, MD, chief of emergency medicine at ZSFG. "We're seeing the impact already."

Poetry Meets Health

Can the power of art stop the epidemic of type 2 diabetes striking youth of color and in low-income communities?

In February, UCSF's Center for Vulnerable Populations (CVP) and an arts education organization called Youth Speaks released four new spoken word videos as part of a social media-based public health campaign to end type 2 diabetes in youth. The films, highlighting the work of young poets, have been featured in the *New York Times* and the *Journal of the American Medical Association*.

Called "The Bigger Picture," the campaign aims to get teens to see the diabetes crisis not just as a medical problem but also as a social justice issue tied to stress, poverty, violence, and limited access to healthy, affordable foods. "I've lectured on the social determinants of health for 25 years, and I've never been able to compete in terms of effectiveness with any of these poems," says CVP faculty member Dean Schillinger, MD, chief of the Division of General Internal Medicine. "This campaign works because the youth poets want to defy Big Soda and Big Ag, protect their friends and families, and promote fairness and justice."

In Anthony Orosco's spoken word video "Empty Plate," the Stockton, Calif., native riffs on the fact that migrant families can't afford the produce they harvest. View the film at thebiggerpictureproject.org.

> "There's no question in my mind that class and color are major factors in impairing their survival.... It makes me so angry."

Elliott Vichinsky, MD, to ***Kaiser Health News*** on how lack of access to proper care has reduced life expectancy over the last 20 years for patients with sickle cell disease – most of whom are African American. In 1978,Vichinsky founded a center at UCSF Benioff Children's Hospital Oakland where such patients often live 20 years longer than average, due to advances in screening for early signs of organ failure.

> "We do have snakes in our freezer, and birds. Maybe a polar bear."

UCSF graduate student **Hanna Retallack**, who works in the lab of infectious disease expert Joseph DeRisi, PhD, to ***National Geographic***. Retallack tested the cerebrospinal fluid of one of the thousands of leopard sharks that died in San Francisco Bay last year and identified the parasite *Miamiensis avidus* as the killer.

> "In research, we are explorers. We have no idea where we are going. It is unpredictable."

Peter Walter, PhD, a professor of biochemistry and biophysics at UCSF and a Howard Hughes Medical Institute investigator, to the ***San Jose Mercury News***, after winning a $3 million Breakthrough Prize, the largest monetary award in science. Walter, who conducts research on a biological mechanism that normally protects cells but can cause disease if it's not functioning properly, was also recently named to the prestigious National Academy of Inventors.

PHOTO: JAMIE DEWOLF

In just seconds, the newest dental lasers can alter the chemical composition of tooth enamel, making it stronger.

Let There Be Light

Soon after lasers were invented in the 1960s, dentists wondered if the powerful form of light could be used on teeth. Today's lasers – finely tuned instruments that can remove cavities painlessly or cut soft tissue without triggering bleeding – may be on the cusp of transforming dentistry.

For example, some lasers deliver heat in microsecond pulses, inducing subtle changes in the top layer of tooth enamel. This makes the enamel more resistant to acids produced by oral bacteria – acids that eat away at tooth enamel and instigate cavities.

UC San Francisco has a long association with dental lasers. John Featherstone, PhD, who just retired after 10 years as the School of Dentistry's dean, was known as a pioneer in preventive laser dentistry when he joined UCSF in 1995. And a 2012 clinical study led by UCSF's Peter Rechmann, DMD, PhD, showed that lasers in combination with fluoride varnish can even promote remineralization of already damaged teeth.

Peter Rechmann, DMD, PhD, professor of preventive and restorative dental sciences

Yet despite decades of successful research, Rechmann, a professor of preventive and restorative dental sciences, estimates that fewer than 10 percent of practicing dentists use lasers.

Although prescription fluoride toothpaste can protect and remineralize teeth with daily use, lasers achieve long-lasting benefits with just one treatment. That makes lasers an especially good option for those with braces, which make teeth difficult to brush thoroughly, or those prone to tooth decay.

Dental lasers have another advantage, adds Rechmann – they're "appealing for young patients who are nervous about the drill."

He's now taking the next step by embarking on a large clinical study of preventive laser dentistry. His hope is that the technology will soon be available to many more patients.

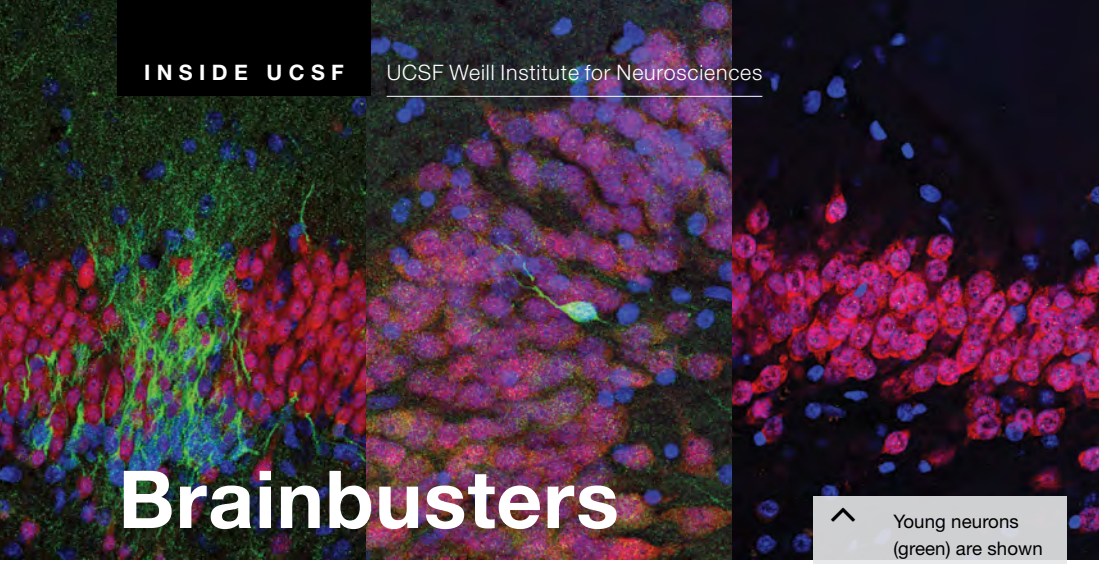
DENTAL LASER PHOTO: JACQWI CAMPBELL; E-CIGARETTE PHOTO: GRINVALDS

E-Cigarettes
Toxic Trouble for Teens

Teens who smoke e-cigarettes are exposed to high levels of some of the same potentially carcinogenic chemicals found in tobacco cigarettes – even when e-cigarettes don't contain nicotine.

A recent UCSF study found that levels of toxic organic compounds were three times higher in teens who use e-cigarettes than in teens in a control group. Mark Rubinstein, MD, a professor of pediatrics, says toxic compounds were even found in the bodies of teens who used flavored e-cigarettes without nicotine. He explains that this is because chemicals in e-cigarettes, like glycerin and propylene glycol, are approved by the Food and Drug Administration for use at room temperature but can produce toxic substances when heated.

Levels of toxic organic compounds were up to 3x higher in e-cigarette users.



Brainbusters

Young neurons (green) are shown in the human hippocampus at the ages of (from left) birth, 13 years old, and 35 years old.

One of the liveliest debates in neuroscience over the past half-century surrounds whether the human brain is static or is able to renew itself by producing new neurons throughout life – a process known as neurogenesis – and, if the latter is true, whether it may be possible to boost the brain's regenerative capacity.

Now, UC San Francisco scientists have shown that neurogenesis declines throughout childhood and is undetectable in adults. They did this by studying the human hippocampus – a region of the brain essential for learning and memory and a key place where researchers have been seeking evidence that new neurons arise throughout an individual's life span.

"We find that if neurogenesis occurs in the adult hippocampus in humans, it is an extremely rare phenomenon, raising questions about its contribution to brain repair or normal brain function," says Arturo Alvarez-Buylla, PhD, whose lab published the new study.

Arturo Alvarez-Buylla, PhD, Heather and Melanie Muss Professor of Neurological Surgery

Alvarez-Buylla, UCSF's Heather and Melanie Muss Professor of Neurological Surgery, is a leading expert in brain development. Over the past 30 years, he has played a key role in convincing the scientific establishment that new neurons arise throughout life in animals such as songbirds and rodents. In recent years, however, the Alvarez-Buylla lab and others have cast doubt on whether neurogenesis persists into adulthood in the human olfactory bulb, as it does in rodents, showing that while new neurons integrate into the human frontal lobe after birth, this process ends during early infancy.

The lab's new research, based on careful analysis of 59 samples of human hippocampus from UCSF and collaborating institutions around the world, suggests that new neurons may not be born in the adult human brain at all. The findings present a challenge to a large body of research, which has proposed that boosting the birth of new neurons could help to treat brain maladies such as Alzheimer's disease and depression. But the authors said it also opens the door to exciting new questions about how the human brain learns and adapts without the new neurons that have been observed in mice and other animals.

Molecular Key to Keto

A ketogenic diet – an extremely low-carbohydrate, high-fat regimen, which can benefit those with epilepsy and other neurological illnesses – may work by reducing inflammation in the brain, according to a study led by Raymond Swanson, MD, a professor of neurology and a resident alumnus. His team identified a protein that, if blocked, can mirror the anti-inflammatory effects of a ketogenic diet. The finding opens the door for new therapies that could reduce harmful brain inflammation following stroke and brain trauma by mimicking the diet's beneficial effects. It's promising news, since such diets can be difficult to follow, especially by those who are ill.

High Anxiety

Have you ever felt an irresistible urge to step back from a high ledge? UCSF researchers may have found the neurons responsible for such deep-seated anxieties.

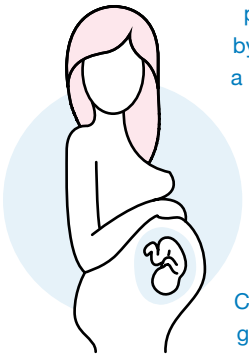
Live imaging of the brains of mice in a maze revealed neurons in the hippocampus that respond when mice wandered near drop-offs or into open areas – places that typically trigger anxiety in rodents. The scientists showed that these neurons connect directly to another region of the brain, in the hypothalamus, that triggers avoidance behavior in animals.

The team, led by Mazen Kheirbek, PhD, an assistant professor of psychiatry, used beams of light to control the pathway from the anxiety neurons to the hypothalamus. They found that suppressing the pathway made mice more comfortable in frightening environments, while stimulating it induced anxiety even in mice in safe spaces. The discovery of hard-wired anxiety circuits could help illuminate anxiety disorders in humans and potentially lead to improved therapies.

CELL IMAGES: ARTURO ALVAREZ-BUYLLA LAB; KETO PHOTOS: MAGLARA

Unraveling One of the **Big Mysteries in Science**

Preterm labor, a common pregnancy complication, has long been a mystery to scientists. But a new study from UCSF shows it may sometimes happen when the fetal immune system "wakes up" too early and begins to reject the mother, causing the uterus to start contracting.



More than one in 10 pregnancies are affected by preterm labor, in which a baby is born earlier than 37 weeks of gestation.

Preterm birth is the leading cause of infant mortality in the United States and the world. Children who survive may go on to face a lifetime of health problems.

The researchers think the fetal immune system becomes triggered in a case of mistaken identity. An initial infection in the mother can result in inflammation and arouse the fetal immune system. The fetal immune cells confuse the mother's cells for an invader and mount an attack, in the form of inflammatory chemicals. These chemicals then trigger contractions, leading to preterm labor, the leading cause of infant mortality.

"The dogma has always been that the fetus has a very immature immune system, and as a result, people haven't really considered its possible role in pregnancy complications," says senior author Tippi MacKenzie, MD, an associate professor of surgery. "We showed that in patients who have preterm labor as a result of some kind of infection or inflammation – the most common cause of preterm labor – the fetal immune system awakens prematurely and may trigger labor."

Tippi MacKenzie, MD, associate professor in the UCSF Division of Pediatric Surgery and the Fetal Treatment Center

MacKenzie, a member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, has long studied the fetal immune system in the context of fetal stem cell transplants. She became interested in preterm labor during her own pregnancy, when she experienced a long period of bed rest because she was at risk of delivering her baby early.

"The medicines we use to treat preterm labor right now are just aimed at stopping the uterus from contracting. But at that point, the horse is out of the barn," MacKenzie says. "What we really have to do is diagnose and treat fetal immune activation, which is probably starting weeks before the patient comes in with the uterine contractions."

Her lab is now pursuing biomarkers in the mother's blood that can identify whether the fetal immune system is activated and beginning to increase the risk for preterm labor.

ICON: ICONICBESTIARY; PORTRAIT PHOTO: STEVE BABULJAK; PHOTO: PIXELISTANBUL

Life After the Diagnosis: Expert Advice on Living Well with Serious Illness for Patients and Caregivers

This new book by international palliative care expert and UCSF physician **Steven Pantilat, MD '89**, serves as a guide for those who don't know where to start at a difficult time. Pantilat makes sense of what doctors may say, what they actually mean, and how to get the information you need to make the best medical decisions.
Read: *bit.ly/ucsf-read-s18*

Grad Slam: "Don't Go Breaking My Heart … Again"

This UC San Francisco competition challenges PhD students to use engaging "nonspecialist" language to describe their intricate research – in three minutes or less. Bioengineering student **Yiqi Cao** won the top prize this year for her talk about how to improve stents to reduce scar tissue. "Grad Slam was an incredible opportunity to challenge myself," Cao says. "It's definitely not easy to distill … many years of research down to a meaningful three minutes."
Watch: *bit.ly/ucsf-watch-s18*

NPR's *Nerdette* podcast: "I Have A Rare Genetic Disease. CRISPR Might Fix It."

As a kindergartener, *Nerdette* co-host Greta Johnsen was diagnosed with an eye condition that is among the best diseases for experimenting with the gene editing tool CRISPR. This episode follows Greta, her father, and UCSF geneticist and Gladstone Institutes investigator **Bruce Conklin, MD**, as he tries to develop the perfect CRISPR system to remove the faulty DNA from Johnsen's eye cells.
Listen: *bit.ly/ucsf-listen-s18*

Tops in Nation for Education

UCSF's School of Medicine placed in the top five nationally in this year's *U.S. News & World Report* survey of the best graduate and professional schools. UCSF was the only medical school to be ranked in the top five in both biomedical research and primary care. The University's biomedical science PhD programs were among the top 10, and the School of Nursing was 11th overall among nursing master's degree programs. Although UCSF also has top schools of dentistry and pharmacy, *U.S. News* does not rank dental schools and did not rank pharmacy schools this year.

"Among the many things that UCSF does, education is at its core," says UCSF Chancellor Sam Hawgood, MBBS. "California and the nation look to us to train the next generation of doctors, nurses, dentists, and pharmacists, as well as the researchers who will advance each of these fields, and our faculty rise to the challenge every year."

ICONS: PICONS.ME; PHOTO: ELENA ZHUKOVA

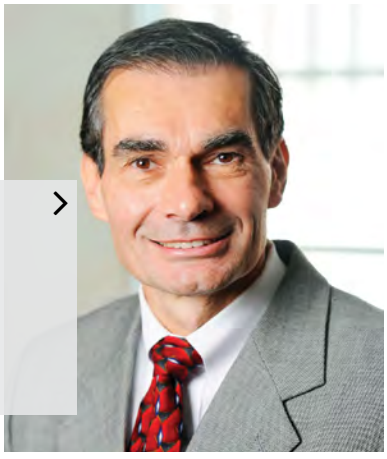
Apple Watch Can Detect Atrial Fibrillation

Atrial fibrillation – irregular heartbeats that may cause strokes – can be detected accurately using an Apple Watch app, according to a recent UCSF study.

"Given the broad and growing use of smartwatches and the ready accessibility of downloadable mobile apps, this approach may ultimately be applied to efficiently screen for atrial fibrillation," says senior author Gregory Marcus, MD, MAS '08.

Gregory Marcus, MD, MAS '08, director of clinical research for the UCSF Division of Cardiology

A leading cause of stroke, atrial fibrillation often shows no symptoms and can remain undetected until a stroke occurs. Earlier detection would allow doctors to administer clot-busting medication to mitigate the risk of stroke and other complications, Marcus says.



"I believe in building a culture that embraces the uniqueness of each individual and fosters a collaborative environment for faculty, staff, and students to succeed."

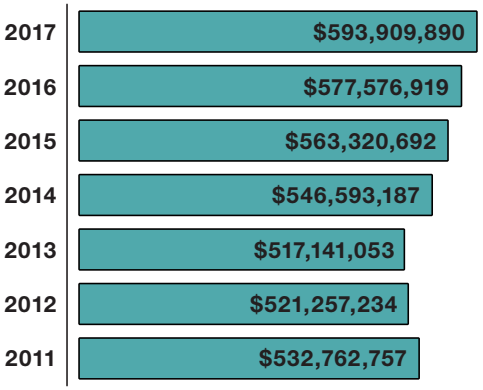
Reddy Named Dentistry School Dean

Michael Reddy, DMD, DMSc, an internationally renowned periodontics specialist, is joining UCSF in June as dean of the School of Dentistry. Reddy spent the previous 29 years on the faculty at the University of Alabama at Birmingham School of Dentistry, including the last seven years as dean. Reddy succeeds John Featherstone, PhD, who led the school as interim dean and then dean from July 2007 through the end of 2017. Mark Kirkland, DDS, associate dean for clinical affairs, was named interim dean for the six months between Featherstone's departure and Reddy's arrival.

WATCH PHOTO: SHANNON FAN; REDDY PHOTO: COURTESY OF UNIVERSITY OF ALABAMA AT BIRMINGHAM

Seven-Year Streak at No. 1

In fiscal year 2017, UCSF received more biomedical research funding from the National Institutes of Health (NIH) than any other public institution, continuing a seven-year streak. In addition, UCSF was the second-highest grant recipient among all public and private institutions nationwide. UCSF's schools of Medicine and Pharmacy ranked first among their peers nationwide in NIH funding for biomedical research and graduate-level training, while the schools of Dentistry and Nursing ranked second in their fields.



Alan Ashworth, PhD, president of UCSF Helen Diller Family Comprehensive Cancer Center and Heise Distinguished Professor, was elected a fellow of the American Association for Cancer Research Academy. Ashworth was part of the team that identified the BRCA2 gene, and he later discovered an innovative way to treat BRCA2 cancers.

Patricia Babbitt, PhD '88, professor of bioengineering, was named a fellow of the International Society for Computational Biology. Her election recognized Babbitt's pioneering contributions to improving understanding of the activity of individual enzymes and their evolution.

Barbara Drew, MS '80, PhD '90, professor emerita of physiological nursing and founder of the School of Nursing's ECG Monitoring Research Lab, was inducted into the American Nurses Association Hall of Fame. Drew was honored for her work in electrocardiography, which has improved the care of patients with cardiac arrhythmias.

Ying-Hui Fu, PhD, and **Andrej Sali, PhD**, were elected to the National Academy of Sciences, one of the highest honors accorded to American scientists. Fu, a professor of neurology and a member of the UCSF Weill Institute for Neurosciences, studies the genetic basis for human circadian rhythms and sleep behaviors. Sali, a professor of bioengineering, studies the structure, function, and evolution of proteins and their assemblies.

PHOTO: BARBARA RIES

The anguished wail from two-time Oscar winner Frances McDormand touched a nerve among the several hundred people gathered for an event titled "Sudden Death by Illness, Injury, or Choice" at UCSF's Cole Hall. Playing the role of Tecmessa to actor David Strathairn's Ajax, McDormand was mourning the death of her beloved husband, who ignores her pleas and impales himself on his sword.

Bryan Doerries, co-founder and artistic director of Theater of War Productions, brought Sophocles' *Ajax* to UCSF on April 18, using the 2,500-year-old Greek tragedy to start a conversation with the university community about facing death both professionally and personally. Tears flowed during the dialogue following the reading, and many nodded when a third-year medical student asked, "How can I deal with the deaths of my patients day after day after day, when I can barely deal with my own father's death?"

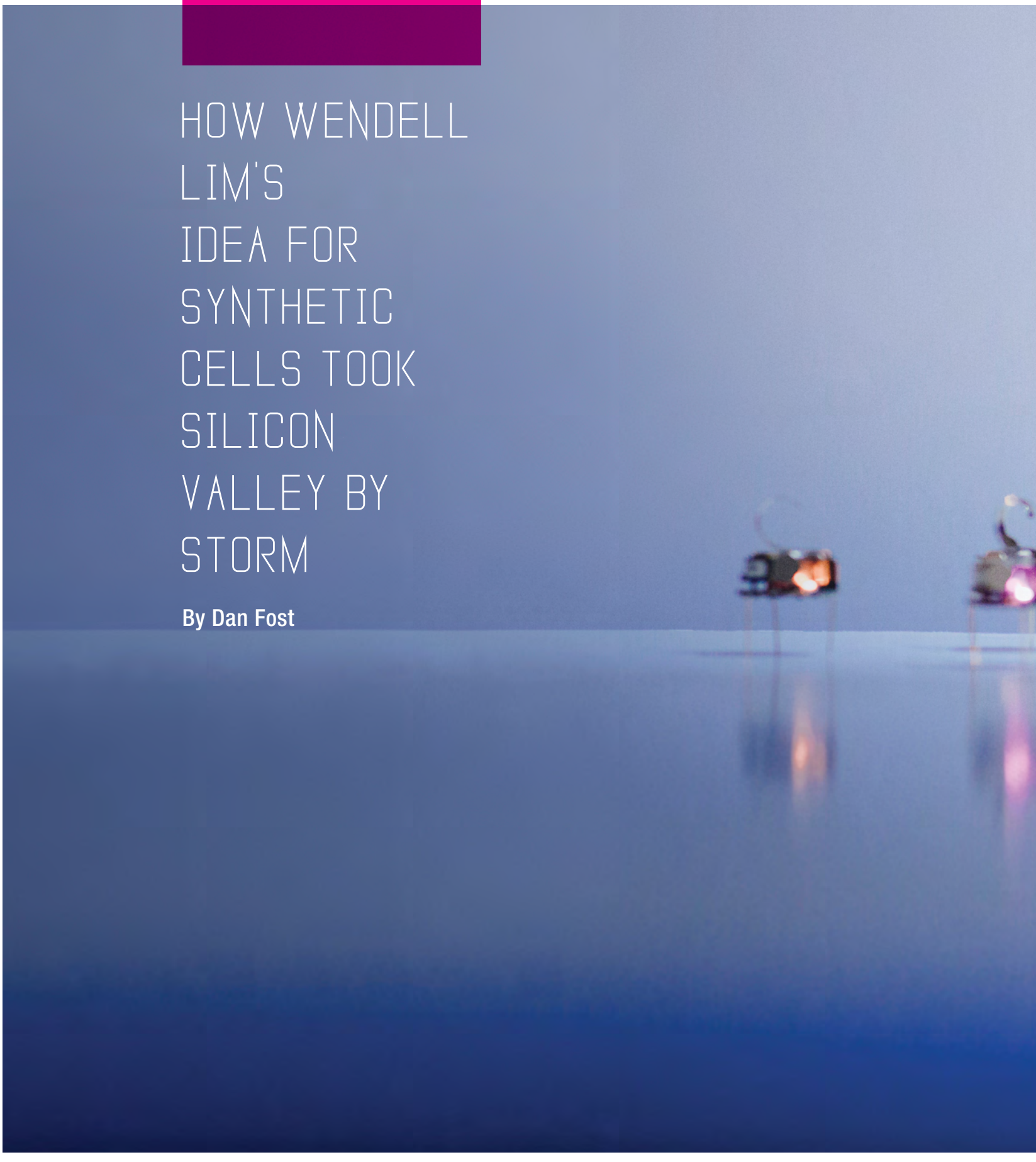
The answers – talk to one another, support each other – came both from the audience and from a panel featuring UCSF Executive Vice Chancellor Daniel Lowenstein, MD; geriatrician Rebecca Sudore, MD '99; UCSF medical student Tiana Woolridge; and Ken Baldwin, a high school teacher who jumped off the Golden Gate Bridge in 1985 and survived.

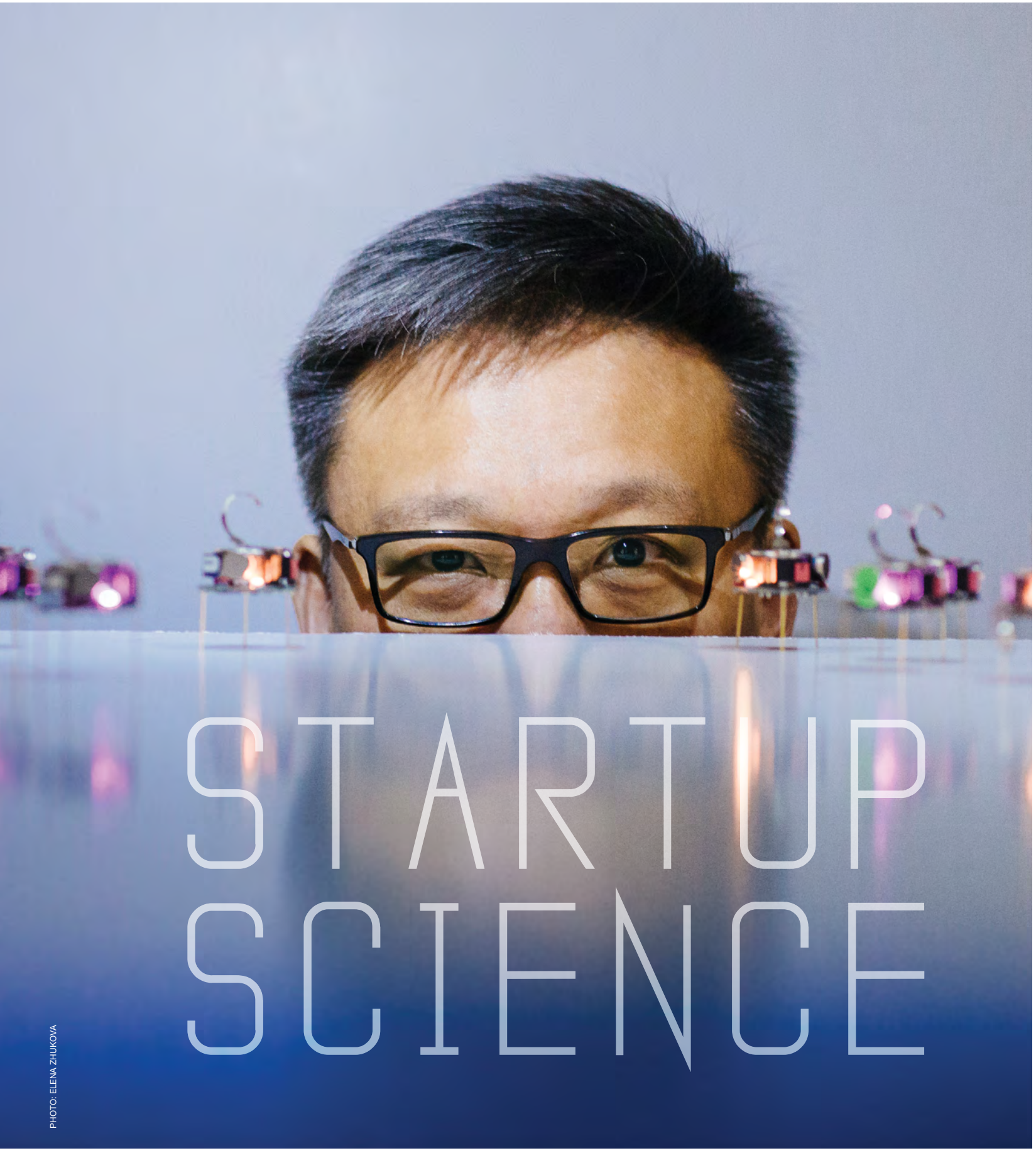
Doerries ended the powerful and poignant evening with what he called his nightly benediction: "You are not alone across time."

– Katherine Conrad

HOW WENDELL LIM'S IDEA FOR SYNTHETIC CELLS TOOK SILICON VALLEY BY STORM

By Dan Fost





STARTUP SCIENCE

PHOTO: ELENA ZHUKOVA

Scientists working on the molecular and cellular level know that big things happen in small systems.

In 2007, UCSF's Kevan Shokat, PhD, parlayed his work on kinases – enzymes that regulate cellular pathways – into a company, Intellikine, which developed small-molecule drugs to fight cancer. Four years later, Takeda Pharmaceuticals of Japan acquired Intellikine for $190 million, boosting the odds that Shokat's discoveries would make it into approved therapies that would reach patients.

When you experience that kind of success, colleagues take notice. So, it turns out, do their spouses.

Wendell Lim, PhD – like Shokat, one of the leading lights in UCSF's Department of Cellular and Molecular Pharmacology – felt a little heat when his wife, Karen Earle, MD, heard the news of Shokat's success.

"That's really cool," she said. "You should do that."

Lim laughed, he recalls. "My work is not like that," he told her, explaining that "Kevan is a chemist – a chemical biologist who develops small-molecule drugs." It's much more common for someone like that to have industry take their work and apply it to patients.

Lim saw himself differently. He's a basic scientist. He's not finding cures or designing drugs. He's following his curiosity. He's pushing the frontiers of human knowledge. If anything, he's a scientist with a passion for art – someone who nearly chose an artist's life and still loves to paint, draw, and make prints and who brings creativity to his work in the lab.

Well, he *was* strictly a basic scientist, until his work started revealing a translational side. That knowledge he's uncovering? It might save lives, it turns out. As Lim pressed on with his study of the science of cells, seeking to understand their secret programming language – the way they send and receive signals to control all the important things happening in the human body – he started to take his insights to the next level. He figured if he knew how cells were programmed, then perhaps he could reprogram them. He even developed ways to create new synthetic cells, which he believed could act like tiny robots inside the body, aiding the immune system as it fights cancer cells.

That, it turned out, was an idea the biotech industry could get behind.

In 2014, the University, Lim, and several of his postdocs and other colleagues patented some of the discoveries from his lab. Venture capitalists and others began lining up to fund the creation of a company almost immediately. In 2015, Lim teamed up with a blue-chip group of investors to establish Cell Design Labs (CDL), which raised $34 million in venture capital. In what industry observers say was a head-spinning turn of events, biotech giant Gilead Sciences acquired CDL in December 2017 in a deal worth at least $175 million – and as much as $567 million if certain milestones are met.

While Earle believed in Lim's scientific abilities, she hadn't been seriously prodding him to follow in Shokat's footsteps. And her offhand comment didn't cause Lim to pursue translational medicine and start a company. He and his team simply followed the science, and, in this case, it led them to breakthroughs that could have a real impact for patients.

Noble aims

Like Lim, most academic scientists who launch companies or license their work to the private sector are motivated by far more than the potential payout. Instead, they understand that companies have the resources and expertise to get drugs, therapies, technologies, and other solutions out of the lab and into the marketplace, where they can help patients. Companies can raise money; navigate the regulatory process; fund expensive, late-stage clinical trials; and bring products to market.

"University labs excel in basic chemistry and biology, but the task of testing potential drugs in humans – or otherwise demonstrating proof of concept and building real value – falls to industry," says Harold "Barry" Selick, PhD, UCSF's vice chancellor for business development, innovation, and partnerships.

Biotech and pharmaceutical companies increasingly look to academia for groundbreaking discoveries that could fuel their next big advance in patient care. In the Bay Area, where venture capitalists mint millionaires, and tiny tech startups turn into $1 billion unicorns, creative people with great ideas frequently become successful startup entrepreneurs – and health sciences professors are no exception.

The speed at which Lim's work moved from idea to company to buyout was dizzying.

Lim is only the latest of a number of UCSF scientists who have turned the intellectual property developed in their labs into companies that became hot acquisitions. In 2017, UCSF scientists logged 233 new inventions, received 56 newly issued U.S. patents, started 13 new companies, produced 97 technology licenses, and generated $25.2 million in licensing income for the University. (See "Successful Spin-offs," page 18.)

But even in the context of those numbers, the speed at which Lim's work moved from idea to company to buyout was dizzying, especially considering the size of the deal. In many ways, that deal helps validate a big bet UCSF is making: that an ambitious internal investment program will help its scientists develop and bring their discoveries to patients quickly. In 2017, Selick, a former UCSF postdoc, returned to the University after a successful career in biotech. He now runs UCSF's newly created Innovation Ventures, a broad

initiative designed to encourage scientists to build greater value in their programs before partnering with industry or starting a company. (See "Unleashing Entrepreneurs," below.)

Rock star

Lim, who succeeded Shokat as chair of the Department of Cellular and Molecular Pharmacology (and, like Shokat, is an investigator with the prestigious Howard Hughes Medical Institute), has described his work as ripped from the pages of science fiction.

Selick was at a meeting of academic and industry leaders where Lim was a featured speaker, holding the group in thrall. "The guy's a rock star," Selick says. "The way he thinks about engineering cells is the way anyone else thinks about building with Legos."

Lim, who is also the Byers Distinguished Professor, holds several patents; his lab helped develop CRISPRi, CRISPRa, and other pioneering genetic technologies. These advances took CRISPR, which has been called "the world's most versatile gene-editing tool" and one of the most exciting biological discoveries of the past decade, and enabled scientists to do more than merely edit genes – now they could control them. CRISPRi allows for "interference," or switching genes off; CRISPRa allows for "activation," or turning them on.

Taking that project to the next level, Lim started creating customized cells that scientists can program. He began looking at T cells, immune system components that attack harmful invaders.

Doctors have been experimenting with using patients' own immune cells to treat their cancer. The most promising results so far have come when scientists engineer chimeric antigen receptor (CAR) T cells to attack certain blood cancers. So Lim and his team set out to gain more control over CAR T cells, in the hope that they would tackle solid tumors. They tried using small-molecule drugs to harness CAR T cells' power, hoping to avoid potentially lethal side effects.

At the same time, Lim set an even more audacious goal: to find a solution beyond drugs. "Really, our dream is to have cells that are like natural cells," he says. "Natural cells don't need to be told what to do. They're very smart. They're like autonomous vehicles. They can look at lots of situations and know what to do."

In Lim's dream, an autonomous cell would attack cancerous antigens without attacking healthy cells.

To get there, Lim and his collaborators – including one of his former postdocs, Kole Roybal, PhD, who is now on the UCSF faculty and who won the Sartorius & *Science* Prize for this work – first developed "on-switch" technology, which can control when therapeutic proteins are activated, or switched on. Then they had another breakthrough, devising something they called synNotch receptors, which, according to an online forum run by the publication *Ars Technica*, "might well be the next great revolution in cancer therapy."

The term synNotch is shorthand for "synthetic notch," with notch being a specific cell surface receptor – a protein that plays a key role

UNLEASHING ENTREPRENEURS

When Harold "Barry" Selick, PhD, arrived at UCSF in the newly created post of vice chancellor for business development, innovation, and partnerships, he thought he'd have to ferret out researchers whose projects might have commercial potential. To his surprise, the researchers started finding him.

"For every faculty member I went to, four or five came to me," Selick says. "There is so much pent-up interest in entrepreneurship here, it's almost unbelievable."

Of course, scientists have been starting companies out of UCSF since 1976, when biochemistry professor Herbert Boyer, PhD, teamed up with venture capitalist Robert Swanson to start Genentech, launching the biotech industry. Shortly thereafter, in 1981, Chiron Pharmaceuticals was founded by three UC academics, led by William Rutter, PhD, the Herzstein Professor emeritus at UCSF.

Selick, who completed a postdoctoral fellowship at UCSF at the start of his career, was a beneficiary of that trend. He started out as a successful bench scientist, worked his way into the executive suite, and ultimately co-founded and ran two companies himself, including Threshold Pharmaceuticals, an oncology drug discovery company that he led as CEO from its founding, through its initial public offering, to its sale in 2017.

Now that he's returned to academia, he waxes enthusiastic about the prospects of starting even more companies, finding the sweet spot that both helps patients and generates substantial returns for the University.

"When I did my postdoc here in the '80s, entrepreneurship was almost a bad word," Selick says. Many people viewed industry with suspicion. Now, he says, "that sentiment has almost flipped."

Innovation Ventures aims to accelerate the process of bringing discoveries to patients, in the process helping UCSF achieve its mission of transforming health care.

In the words of Regis Kelly, PhD, director of QB3, the Institute for Quantitative Biosciences on UCSF's Mission Bay campus: "It's a big goal: Make UCSF the premier life sciences entrepreneurship campus in the country."

Barry Selick

PHOTO: NOAH BERGER

in enabling cells to communicate with other building blocks of the body, such as hormones, nutrients, and neurotransmitters. Synthetic means it was made in the lab – part of Lim's goal of creating cells to do specific tasks.

SynNotch receptors represent one of the key technological underpinnings of Cell Design Labs.

Birth of a business

When a scientist makes an important technological advance, as Lim did, that's considered intellectual property – much like a novel produced by an author. But such intellectual property is not protected until the scientist files a patent; without that protection, anyone else could use the knowledge to devise their own therapy. Potential investors want to see a patent before putting their money behind an idea. UCSF has an office of experts to help scientists navigate the world of patent law.

Todd Pazdera, PhD, is associate director of UCSF's Office of Technology Management (OTM) – part of Selick's newly revamped Innovation Ventures organization. Pazdera is a scientist by training whose career took a turn toward business shortly after he received his PhD in biological sciences from Carnegie Mellon University.

"I love the interface between science and business," he says. "Startup development and licensing create a mechanism to translate the science into new products."

That's where OTM comes in. "We say, 'Let's talk about where we can go next,'" Pazdera explains. "'Let's think about how to advance the science to the next stage toward commercialization.'"

Selick says Pazdera played a critical role in getting Cell Design Labs off the ground and eventually sold to Gilead.

Pazdera has been involved in launching many University startups, and he already had a good relationship with Lim. When Lim's experiments in synthetic biology began to bear fruit with the development of synNotch, the conversations expanded.

Lim's work was much further out on the cutting edge than most of what Pazdera sees. "We're doing such new stuff that there's not a lot of appreciation for what its value is," Lim says. "We're creating what its value is."

It's so new that Lim eventually had to fly to Washington, DC, with a lawyer to educate patent examiners about the technology. The patents were filed in 2014, and then came the next decision: Should they start a company? License the technology?

"Many companies were interested in the technology, including several venture capitalists," says Pazdera, who reviewed the business plans that many of them had submitted.

Some of the bidders wanted to license the technology. Scientists

SUCCESSFUL SPIN-OFFS

The Office of Technology Management at UCSF has facilitated more than 100 start-ups, including these multimillion-dollar deals involving technology that emerged from UCSF labs in recent years:

eFFECTOR Therapeutics invents and develops small-molecule drugs to fight cancer, with a long-term goal of attacking other diseases, too. Founded in 2012 by UCSF faculty members Kevan Shokat, PhD, and Davide Ruggero, PhD, the Diller Family Professor, eFFECTOR has raised nearly $140 million in four rounds of venture capital financing.

Pliant Therapeutics develops therapies to treat fibrotic disorders of the lung, liver, and kidney. It was founded in 2016 by the UCSF research team of Dean Sheppard, MD; William DeGrado, PhD; Harold Chapman, MD; and Bradley Backes, PhD, with $45 million from Third Rock Ventures, LLC.

Pionyr Immunotherapeutics harnesses the body's own antitumor immunity. Max Krummel, PhD, UCSF's Smith Professor of Experimental Pathology, co-founded the company in 2015 with Sachdev Sidhu, PhD, a former Genentech protein engineer now at the University of Toronto. In December 2017, Pionyr announced a $62 million Series B round of investment.

Relievant Medsystems designs medical devices that use nerve ablation to treat chronic low back pain. Founded in 2006 by UCSF's Jeffrey Lotz, PhD, the Bradford Professor of Orthopaedic Surgery, and Christian Diederich, PhD, a professor of radiation oncology, the company has raised more than $95 million over the years, including $36 million in equity financing in 2016.

Neurona Therapeutics applies stem cell research to the treatment of neurological diseases. Its UCSF co-founders were Arturo Alvarez-Buylla, PhD, the Muss Endowed Professor; Arnold Kriegstein, MD, PhD, the Bowes Distinguished Professor; John Rubenstein, MD, PhD, the Ireland Distinguished Professor; and Cory Nicholas, PhD '09, an adjunct assistant professor of neurology. The company was launched in 2015, having raised more than $31 million.

Fortis Therapeutics develops new antibody drug conjugate therapies for late-stage cancers. It was founded in 2016, based on technology developed by Bin Liu, PhD, a professor of anesthesia and perioperative care, and raised $18 million in Series A financing.

often see an advantage to licensing, in that a company will have the resources to move the technology forward and the scientist can stay in academia, without the headache of running a company. But scientists often worry, if they license their innovation, whether they'll lose control of it. Will its new owner have the same drive to champion the technology as its creator?

Lim had another concern, because his technology was so new and complex: "If people didn't understand it, would they really push it and keep developing it?"

"That," he says, "is where the idea came from that we really need to start our own company."

Given the Bay Area's entrepreneurial ecosystem, Lim's work quickly attracted investors and $34.4 million in financing. In June 2016, Cell Design Labs set up shop at an incubator just south of UCSF's Mission Bay campus.

One critically important early investor was Kite Pharma, which was doing similar work with therapeutic cells. Kite, a publicly traded company headquartered just west of Los Angeles, in Santa Monica, not only invested in CDL but also established a research collaboration with the newly formed company.

"What's fun for me now is realizing just how much creativity is required in science. Whenever you put together a piece of work, it's really a big canvas."

– Wendell Lim

Moving fast

Within six months of its founding, CDL moved to Emeryville, across the bay from San Francisco. In its first two years, the company grew to 70 people.

Then, in August 2017, Gilead Sciences – founded and headquartered in the Bay Area and one of the world's largest biotech companies – bought Kite for $11.9 billion. Kite's founder and CEO, Arie Belldegrun, MD, a highly regarded industry veteran, was close to CDL's leadership, Pazdera says.

"Kite knew Cell Design Labs very well and appreciated the power of the technology, and they convinced Gilead to get interested, and that's how the sale happened," Lim says.

The deal – which went from filing a patent in December 2014 to establishing a startup in December 2015 to an acquisition in December 2017 – was one of the quickest Pazdera has seen in his 15 years in the field.

It helped that the field of immuno-oncology, or using the immune system to attack cancer, is particularly hot right now. But perhaps most important was the scientist behind the technology. Lim's hands-on involvement showed investors that this was "real-deal, cream-of-the-crop stuff," Pazdera says. And when Gilead showed an interest, Lim played a major role in educating them about the company and the potential of its technology.

Even after the sale, Lim continues to work as an adviser to Cell Design Labs, and he keeps pushing the work forward in his own lab at UCSF.

An artist, too

When Lim was a high school student in Chicago, he was already showing an aptitude for science. The son of physician-scientists at the University of Chicago, Lim was a Westinghouse Science Talent Search finalist, earned degrees from Harvard and MIT, and was a postdoctoral fellow at Yale. Ever since arriving at UCSF in 1996, he has astounded the scientific community with the cellular insights and innovations emerging from his lab.

Yet since childhood, Lim has always loved art, too. He met Earle, his wife, in an art class at Yale. Even as he pursued his career in science, he never stopped creating art.

"We both have a passion for art," Earle says. "Painting, drawing, sketching are all outlets for Wendell."

Lim now uses his art to communicate what's happening in the microscopic world in which he performs his science.

"People don't understand what we do," Lim says. "That's a big issue. Our world's not that different, it's just really small. We know it, but how do we let other people know about it? I've been experimenting with different ways to do that."

His lab website is chock-full of these efforts, including bright, whimsical cover art that he has had accepted by scientific journals. For one on "orchestrating cell signaling with optogenetics," he drew a Matisse-like cellist and a Cubist guitar. For another, on "scaffold regulation of MAPK signaling," he showed workers in hard hats at a construction site's scaffolding, as green, blob-like molecules are hoisted into place.

His website also features some of his paintings; lately, Earle says, Lim's abstract paintings "are almost molecular in nature."

Lim even designed the logo for Cell Design Labs, in which small white gears engage on a field of orange, evoking neural synapses clicking into place. Such projects are one way he keeps his artistic chops alive.

"What's fun for me now is realizing just how much creativity is required in science," Lim says. "Whenever you put together a piece of work, it's really a big canvas. You have to think about composition, what it means to you, what it means to other people. It's pretty interesting. The brushes are just a lot bigger."

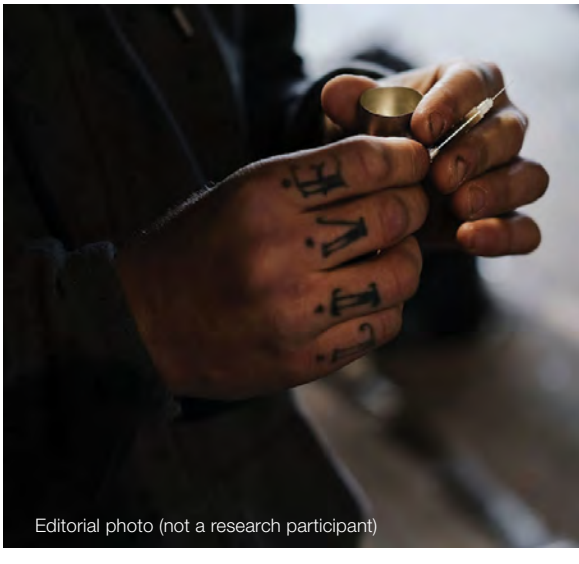
Dan Ciccarone has been studying street-based drug use for 18 years.

PHOTO: LAWRENCE RICKFORD

Streets of Pain

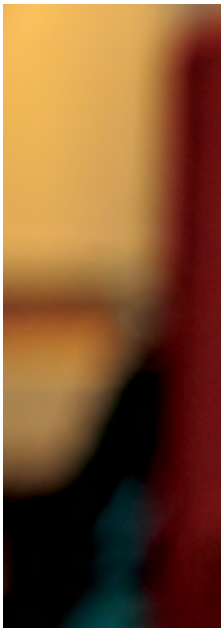
UCSF public health researcher Daniel Ciccarone, MD, shares his quest to understand the nation's opioid epidemic, one user at a time.

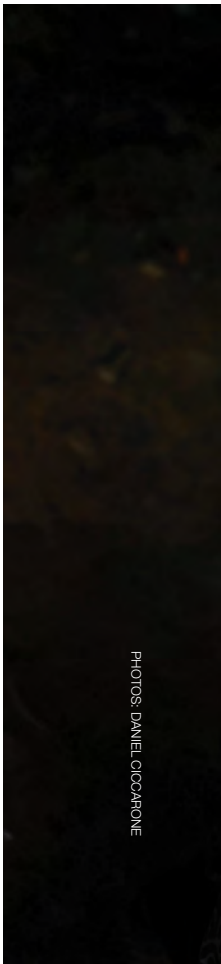
Adapted from a video interview.



Editorial photo (not a research participant)

TOP PHOTO: DANIEL CICCARONE; BOTTOM PHOTO: SPENCER PLATT





PHOTOS: DANIEL CICCARONE

I've been studying the problem of street-based drug use for 18 years. I'm currently the principal investigator of Heroin in Transition (HIT), a five-year study funded by the National Institutes of Health.

HIT's objective is to better understand the heroin crisis. The study involves multiple disciplines, some of which are quantitative, like economics and statistical modeling. But it also has a qualitative component, which draws on medical anthropology and ethnography. We spend time with folks who use heroin and talk with them about their drug use. We want to understand, really understand, the lived experience of those who are experts in heroin: the users themselves.

We do this work in alleyways, in boarded-up buildings, in dank places that often smell of urine, because that's where the action is. We want to watch it happen in its natural setting, to learn from the real world.

Our nation's heroin and opioid crisis has become more and more horrific. Drug overdose deaths now exceed those caused by car accidents and gun violence. It's a complicated problem, because heroin comes into the United States from many sources. Each source has a different chemistry, is used in different ways, and leads to different public health consequences, from HIV to endocarditis [an infection of the heart valves or inner lining of the heart]. And most devastatingly, many sources are now contaminated with fentanyl and other cheap synthetic heroin analogs. These synthetics are causing wave on wave of medical consequences – including overdose deaths, since they're many times stronger than street heroin.

Our street-based research is both the most poignant and most rewarding part of our work. My team and I go all around the country – to big cities and small towns alike – and identify and talk with folks affected by heroin and the new synthetics. We're looking for indigenous insights into this crisis.

The data portion of our work is important, but this qualitative work offers insights we simply can't get from statistics. In 2016, 64,000 people died of drug overdoses. But if we focus just on the numbers, their voices are lost. Who were those 64,000 people as individuals? What led them to use? Why did they die?

States with highest rates of death from drug overdoses in 2016:

West Virginia
Ohio
New Hampshire
Pennsylvania
Kentucky

64,000: Deaths from drug overdoses – of which opioids are the main driver – in 2016.

Statisticians don't get to "why" questions, but ethnographers do. So our ethnographic work helps us understand what leads individuals to do things that put them at risk. Then we can circle back and put those risk factors in a statistical model.

We've engaged with a wide range of people affected by this epidemic: Folks who've been using heroin for three months and folks who've been using for 60-plus years. Young people and old people. People living on the streets and people with jobs. White and black. Rural and urban. We've talked with moms and dads who've lost children to overdoses. We talked with a man in West Virginia who's lost half of his high school class to pills and heroin.

This qualitative work, while it's really rewarding, is also challenging. Because drug use is illegal and highly stigmatized, drug users are difficult to find. We recruit them at needle exchange programs, at clinics, at public health agencies. We try to gain their trust; they usually agree to talk with us and introduce us to their social circle. Then we go sit with them wherever they hang out – in alleyways, in their homes, in their cars – and we talk.

I'll often start by asking what drugs they use – a typical doctor question. Then I'll get into more disarming questions – say, "Tell me what you like about the drug you use." That's a question someone in law enforcement wouldn't typically ask; it shows I'm genuinely interested in the person. Then I might ask, "What brought you to this neighborhood?" or "Tell me how you go through your day."

We always ask open-ended questions, not leading questions. This is just like in a clinical encounter, when we are trying to build rapport and get the patient's perspective. And we'll say "I want to hear about your experience – you're the expert, not me."

Editorial photo (not a research participant)

TOP PHOTO: DANIEL CICCARONE; BOTTOM PHOTO: SPENCER PLATT

Ciccarone calls the current crisis a "triple wave epidemic."

First Wave was the prescription painkiller epidemic, in which powerful opioids were prescribed at alarming rates, causing mass dependency issues that continue today.

Second Wave made landfall in 2010, as former prescription drug patients and other new users came into heroin use, leading to a tripling of heroin-related overdoses since then.

Third Wave has arrived in the form of new, and alarmingly powerful, synthetic opioids.

We ask some fairly intimate questions. But once we've built rapport, we're in. They let us in because we show we care about them and their concerns. I try to approach everyone as nonjudgmentally as I can – as a witness, not an examiner.

And when people hear our questions – and our responses to them, such as "I'm sorry to hear that" or "I'd like to hear more about that" – they can tell we come from a neutral place. These folks don't feel heard by society. They often don't feel heard at the doctor's, for example. They certainly don't feel heard by the legal system. We're trying to give them a voice. When they perceive that from our questions, from our whole process, they open up and tell us stuff – stuff we plan to turn into papers, into tweets, into newsfeeds, into political action and policy changes that will turn around this crisis.

Sometimes I'm asked if I ever feel afraid. We do go places that can be pretty disturbing – abandoned buildings, hovels, secluded alleyways – places not fit for human habitation. We see peeling wallpaper, mattresses on the floor, detritus everywhere. We see and smell evidence of incredibly poor hygiene, evidence of sexual activity. I've even seen knives and guns. It can feel edgy. But we always go in teams of two or three; if any member of a team doesn't feel safe, we don't go. And we never go anyplace we haven't been invited.

There's something about being with people in their everyday environment that helps them open up. Say you're in the habit of going to a café and sitting down over a cup of coffee or tea – that would feel to you like a natural place for a conversation. So being with these people in the places where they hang out with their friends, where they buy or use drugs, feels natural to them.

We're trying to document reality for these folks. Typically we have recorders running, though sometimes we take furious notes after we leave. We record them making the solution, bringing it up into the syringe, and then injecting it. We document the entire process so we can look for micro-practices that might be risky or that might be protective.

We're now three years into HIT, and we've learned a lot – some of it commonsensical, some of it shocking. The level of despair in certain parts of the country is unfathomable.

But at the same time, we've learned that there's tremendous resilience out there. People are learning to deal with this poison called fentanyl. Remember, fentanyl is typically not something drug-users choose – it's a contaminant of heroin. With any given drug purchase, people don't know what they're getting. It's sadly like "Russian roulette." So people have developed ways to test their drugs, to change their behaviors, to try to stay safe. These things are happening organically, not through public health interventions. But could we turn them into public health interventions? I certainly hope so.

That's why it's important to remain curious, both about what we observe and about what those observations may hold in terms of outside-the-box solutions.

Heroin

An opioid drug made from morphine, a natural substance taken from the seed pod of the various opium poppy plants grown in Southeast and Southwest Asia, Mexico, and Colombia.

Opioids

A class of drugs that includes the illegal drug heroin as well as pain relievers available legally by prescription.

Fentanyl

A synthetic (human made) opioid analgesic that is 30-50 times more potent than heroin and 50-100 times more potent than morphine.

Dan Ciccarone conducts field research across the country.

People also ask me what it's like to do this work. I grew up in the streets of New York, so I'm a pretty tough cookie. But it's important to find a balance between being tough enough to go into these places and see what we see, yet do it with a kind of softness and humility that allows us to be receptive to really hearing people's stories.

When I'm in the street, I become a different person. I actually feel different when I'm out there. When I walk into clinic wearing a white coat, I feel a sense of professionalism, a certain sense of hubris as a doctor. But when I go out in the field, I do the opposite. I try to go in as humble and simple as possible. I might wear black if I feel that would fit with the scene. I sit lower than everyone else; I'll often sit on the floor, even if it's filthy. I'll try to make eye contact if it seems welcomed, or I'll avoid eye contact if that seems best. I might even ask questions from across the room, if that's what it takes to make the person feel comfortable.

I truly don't have much fear or concern working with this population. I love what I do. I believe I'm the right person for the job. In fact, doing this research allows me to fulfill multiple parts of myself. I get to be an engaged clinician, and I get to stay curious. I can imagine paths I could have taken where my native curiosity would have been squelched, but this research, diving into this hard problem, keeps me alive. It's a pessimistic problem, but I'm an optimist. And I'm optimistic that we'll find solutions, especially to the stigma and the prejudice.

Stigma is a huge barrier in our society. I think a generation or two from now, we'll be embarrassed by how we currently regard drug use. We're now getting insights from neuroscience, for example, about how addiction is a brain disease, how it rewires people's neural pathways. We want to end the stigma for this highly misunderstood population and problem. I predict that we'll be out of the blame game in a generation or two – which will lead to better policies.

Unfortunately, this epidemic isn't going away any time soon. That's one of the saddest insights I have. For example, you might wonder why a deadly chemical like fentanyl is used by drug lords – wouldn't simple economics lead them to say, "Whoa, we're losing our customer base." But it appears more users are coming in than are passing away; I don't have proof of that yet, but I think it's the case. That's the most horrible thing we've discovered.

We need to stem this crisis, and then we need to reverse it. That's why we are identifying the strategies that people are using to stay safe.

Daniel Ciccarone is a professor of family and community medicine and resident alumnus. Hear his story in his own words in our slideshow at **tiny.ucsf.edu/streetsofpain**. ■

TOP PHOTO: DANIEL CICCARONE; BOTTOM PHOTO: LAWRENCE RICKFORD

The Crisis in Our City

Matthew State, MD, PhD, chair of UCSF's Department of Psychiatry, is playing a key role in an ambitious effort to tackle San Francisco's dire homelessness problem. He answers some tough questions about the challenge.

By Katherine Conrad

PHOTO: ELENA ZHUKOVA

In recent years, homelessness has moved from the periphery to seemingly every street corner. Despite determined efforts by many to fix the crisis, it only seems to worsen. Is it an intractable problem?

No, I don't believe it is. It's a persistent problem, but this is a city that has taken on enormous problems before. During the worst days of the AIDS crisis, academia, philanthropy, the nonprofit community, and government came together to attack what seemed to be an insurmountable challenge. This is the model we are following now in our effort to solve homelessness. We have a committed and diverse community willing and ready to get to work together, and I am proud the psychiatry department and UCSF are contributing to this effort.

You're a renowned expert on the genetics of autism. Why are you focusing on homelessness?

I'm the chair of the psychiatry department at a leading public institution. We take care of people with psychiatric illnesses and substance use disorders. These are individuals who unfortunately are dramatically overrepresented among the homeless. The homeless population in San Francisco numbers more than 10,000 people, and conservatively between 30 percent and 40 percent suffer from mental illness and/or substance abuse. There is an essential connection between mental health and homelessness, and that makes addressing it a central part of our mission.

You came to UCSF in 2013 after having worked at Yale. Did you know solving homelessness was part of the job description here?

One of the reasons I came to UCSF was that this place is committed to bringing together world-class science and the public mission. It's in our DNA. We staff the psychiatry services at Zuckerberg San Francisco General, our safety net hospital. This is ground zero, where the sickest and most vulnerable people in the city come for care and also happen to be overrepresented among the chronically homeless.

What role does the stigma of mental illness play?

The reality is we don't fully understand what causes mental illness and substance abuse yet, so there's still a pervading belief that "it's a choice, it's a moral failing." It's a fundamental misunderstanding of mental illness when people say that "it's just part of the normal spectrum of human behavior" as opposed to "it's a brain disease." In fact, we know these are brain disorders not unlike Alzheimer's disease. But from the standpoint of public policy and the health care system, in many ways it's worse to have schizophrenia than it is to have Alzheimer's. Few people would say someone suffering from severe dementia has a human right to wander the streets.

How can these attitudes change?

We need to keep up our efforts at advocacy and education. And attitudes will change as we understand the biology of mental illness and substance use disorder better. For instance, real progress in discovering the molecular basis of autism has made a big difference in how society views that condition. We've made tremendous advances in understanding a disorder that once was blamed on "refrigerator mothers."

How is the Department of Psychiatry at UCSF attacking homelessness?

Through our public psychiatry programs, including training residents and fellows. Through services that care for severely mentally ill and addicted patients, and patients in supportive housing and the criminal justice system. In addition to psychiatric care, we offer vocational rehab, staff mental health court, consult with public schools and the SF jail, and provide services for teenagers in the criminal justice system. That's just a small sample of the services we provide.

And through basic science. Some people see the basic science side as dissociated from some of these big societal problems. I don't see it that way at all. I think science is going to transform our ability to take care of folks. If we had more effective treatments, many people would not end up sleeping on the streets. That's the beautiful thing about being here at UCSF. We have an opportunity as one of the world's great medical institutions to attack homelessness at all levels.

How have donors responded?

In many parts of the country, donors might think twice about having their name associated with drug abuse or mental illness. It's clearly not that way in San Francisco. We have had remarkable support for a broad range of psychiatric issues since I arrived here five years ago. This institution and our community of supporters recognize homelessness and mental illness as the crisis of our time.

That's why health equity is a central theme of **UCSF: The Campaign**. Do you know how unusual that is? I've never experienced any other place like UCSF.

What will success look like to you?

When I don't have to say, "We don't have that service right now. We can't get you a bed. There's not an opening in that rehab program. I don't have a doc available for a month or a social worker who can manage that." That's what we live with right now. Both my head and my heart tell me we have no choice but to get up every day determined to do better. There should be no place better than San Francisco for taking care of people who are homeless, mentally ill, or suffering from substance use disorders.

Matthew State is the Oberndorf Family Distinguished Professor in Psychiatry and a member of the UCSF Weill Institute for Neurosciences.

Pursuing Partnerships

UCSF is working toward the day when a person afflicted with serious mental illness has the same expectation of care that a cancer patient has. Matthew State, MD, PhD, believes the path to achieving that goal is in partnerships with government, business, and nonprofit organizations.

Key Partners

State calls **Zuckerberg San Francisco General Hospital** "the beating heart of public psychiatry" at UCSF. Operated by the City of San Francisco, ZSFG is staffed by UCSF faculty physicians and psychologists. The safety-net hospital has 44 acute psychiatric beds and San Francisco's only 24/7 dedicated psychiatric emergency department.

The centerpiece of a system of community care, developed in partnership with the City of San Francisco Department of Public Health, includes **Citywide Case Management**, a division of UCSF's Department of Psychiatry, which provides psychiatric services and vocational training to individuals with persistent mental illness; the **Alliance Health Project**, which offers services and support for the LGBTQ and HIV communities; the **Trauma Recovery Center**; and **Division of Substance Abuse and Addiction Medicine**.

UCSF is also developing a collaboration with **Tipping Point Community**, a nonprofit dedicated to fighting poverty in the Bay Area. Tipping Point seeks to reduce the city's chronic homeless population by half by 2022, through providing housing and working with the public and private sectors to tackle the many causes of homelessness.

The **San Francisco Healing Center** opened this spring, with 54 beds for mentally ill patients deemed unable to care for themselves. This public-private partnership includes the **San Francisco Department of Public Health**, **Dignity Health**, **UCSF Health**, and **Crestwood Behavioral Health**.

The Unbearable Sensation of Being

SOME KIDS FIND EVERYDAY STIMULI EXCRUCIATING. SOME SCIENTISTS ARE FINALLY FIGURING OUT WHY.

By Claire Conway

Cindy was cradling her 9-month-old son, Elias, against her chest when she and a room full of family simultaneously yelled "Surprise!" to an unsuspecting aunt on her birthday. The outburst shot like a bolt of electricity through Elias. He cried for an hour.

Xander, while growing up in the perpetual sensory assault of Manhattan, had to get off the train any time someone with a guitar entered his subway car to play for small change.

Cal had a more enigmatic reaction to stimuli. His mother, Jennifer, points to the floor-to-ceiling windows in her hilltop living room. Rooftops, forests, and the San Francisco Bay spool out for miles. Cal was 2 when they moved here from a small, contained apartment. "We got here and Cal was always running away from me," recalls Jennifer. "He suddenly had all this space and stimulation. He was in sensory overload."

▶ **BEYOND NAILS-ON-A-CHALKBOARD:** Elias, Xander, and Cal all experience extreme reactivity to tactile, auditory, or visual stimulation – a condition known as sensory processing disorder (SPD). Tactile triggers that torment kids with SPD include tags in shirts, wooly sweaters, socks, or an accidental shoulder brush during preschool circle time. Auditory offenses include coffee grinders, the birthday song – surprise or not – and noisy, erratically moving toys. Visual provocations that can set kids off include IMAX movies, crowded stadiums, parking lots, even bikes and tents hanging from the ceiling of a camping store. Whether seen, heard, or felt, what all these sensory inputs have in common is their sudden onset and unpredictability.

For an SPD kid, these experiences are beyond a nails-on-a-chalkboard annoyance. "As soon as these kids can move themselves, they will run screaming from the room when these stimuli reach their world," says Elysa Marco, MD '00, a cognitive and behavioral pediatric neurologist at UCSF Benioff Children's Hospital San Francisco and a member of the UCSF Weill Institute for Neurosciences. Take Xander, who is now 14. He would rather be kicked in his hapkido martial arts class than receive a friendly hug. "It physically hurts when people hug me," he says. This makes his mom, Judy, who is a hugger, think twice before reflexively going in for a hug. And Elias, at age 2, would hold his breath and sit at the bottom of the pool – the silence and water pressure his only solace.

Living in a state of perpetual flight, fight, or freeze in reaction to stimuli – or in constant fear of those reactions' onset – takes a toll on SPD children and their parents alike. The disorder can be profoundly disruptive on every level. As a parent, how do you diaper a child who feels abraded by even a cloth diaper? And if you can't diaper a child, how do you leave the house, much less go to work? As a preschool teacher, how do you manage a student who falls apart every time a block falls or a tambourine is tapped? And as that student, how do you connect with your classmates when you feel compelled to dart under a table to save yourself from that tumbling block or terrifying tambourine?

But as life-altering as SPD is for the children and families affected by it, the disorder isn't included in the Diagnostic and Statistical Manual (DSM), clinicians' touchstone for diagnosing psychiatric conditions. Marco's professional quest is to build a

ILLUSTRATION: JAMES YANG

better understanding of the genetics and the neural underpinnings of sensory-processing differences. It's clear that sensory overresponsivity is shared by many children with genetic or psychological conditions like autism and attention-deficit/hyperactivity disorder (ADHD). Indeed, kids with SPD often struggle with more than hypersensitivity: Some 40 percent of kids with an SPD diagnosis also have dysgraphia, meaning they have such poor fine-motor coordination that they have difficulty writing, and 40 percent also have ADHD (these are not necessarily the same 40 percent). While Marco isn't hung up on labels, she is committed to achieving better understanding and better therapeutic support for children with sensory-based challenges. She's encouraged by signs that the field is moving past the DSM debate to a more genetic and symptom-based approach to caring for such kids – in their homes, schools, and communities.

According to Marco, who is also an associate professor of neurology at UCSF and a resident alumna, many SPD kids acquire an autism label along the way, which helps with insurance coverage. And there is overlap in the disorders. Nearly 90 percent of kids with autism also have sensory processing differences – some underresponsivity and some overresponsivity. However, kids with SPD do not usually exhibit the fixated interests, repetitive motions, and social indifference that are hallmarks of autism. "Kids with SPD are wanting to socially engage, they just can't tolerate it," explains Marco.

▶ **DIAGNOSTIC DEBATE:** Early in her practice, Marco kept seeing kids with what were described as developmental delays; they often had autism diagnoses, too. "I would want to ask these parents about seizures, walking, and language development, but they wanted to know how they were supposed to wash their kids' hair when they couldn't touch their head, or how they could just get them clothed and out the door," recalls Marco.

A distinct SPD diagnosis is not without controversy. Some neurologists and pediatricians think SPD is listed exactly where it should be – under autism. Others argue that the condition doesn't exist at all; for years, clinicians attributed SPD to inadequate parenting. Indeed, every parent of an SPD child has stories of being judged for their parenting by clinicians, loved ones, and strangers alike. "I take Cal to places like a restaurant or party where the volume rises. He just loses it – both imploding and exploding. Or in parking lots, he'll just sit down," says Jennifer. "In these scenarios, we always get comments basically indicating that we are obviously not doing this whole parenting thing very well and that with more discipline and authority, his behavior would change. Honestly, I thought that initially, too. And my confidence as a parent went way downhill."

Instead, Marco believes, sensory differences should be regarded as a function of brain structure and brain activity that's guided by both genetic and environmental influences.

▶ **INDISPUTABLE EVIDENCE:** Marco's practice is now spilling over with SPD kids like Elias, Xander, and Cal. She also has a significant social media presence on a Facebook page devoted to sensory processing disorders. Her contributions there resonate with the page's 85,000 members, who are desperate for answers about their children's seemingly bizarre reactivity. And in her lab, she is scientifically validating the life experience of SPD patients by identifying their brains' unique structure and function and their distinct genetic profiles. Marco and her team have done so with great success by leveraging leaps in imaging technology and cross-disciplinary partnerships.

Her lab's first research breakthroughs were back-to-back papers, published in 2013 and 2014 with UCSF radiologist Pratik Mukherjee, MD, PhD. In the first one, Marco and Mukherjee performed brain-imaging studies on kids with SPD, primarily boys, and compared them against typically developing boys. In the SPD kids, they found abnormal tracts in their white matter, a part of the brain that's essential for perceiving, thinking, and learning. These tracts connect the auditory, visual, and tactile systems involved in sensory processing. It was the first time researchers had identified a biological basis for SPD.

In the second study, they compared structural communications in the brains of boys with SPD and boys with autism. They visualized connections among neurons by tracking water moving through the brain's white matter. When water molecules move in the same direction, connections are thought to be directional and strong, while water going against the flow is a sign of faulty connections.

"The data was so clear. Kids with sensory processing differences just have different degrees of connection efficiency, particularly in the back part of the brain," says Marco. This study was the first to show that kids with SPD have quantifiable and distinct differences in brain function. "These kids are not breaking down in school because their parents are doing a bad job or because they are bad kids," says Marco. "Their brains are wired differently."

Marco's research and social media outreach is now arming parents, teachers, and clinicians all over the country – many of whom had never heard of SPD before – with the tools to diagnose and deliver help to kids earlier. The papers are also a wake-up call for neurologists, pediatricians, family, and friends who have questioned the disorder's existence – a bittersweet validation of what parents of SPD kids already knew. A diagnosis that stands on hard scientific ground gives parents authority to explain rather than apologize for their kids' behavior. But more importantly, it gives them license to forgive themselves – to say "I am not crazy," as Elias's mom, Cindy, puts it. "And this is not my fault."

▶ **A FOUR-PART FRAMEWORK:** That scientific confirmation has shifted the conversation to finding viable treatments. Marco has developed a four-part framework for building a safe, positive world in which SPD kids can thrive. The first two elements – controlling kids' environment and arousal – help parents figure out how best to structure their children's physical and emotional surroundings. The third helps kids master healthier reactivity behaviors through brain training. The last helps kids achieve calmness through medications that soften the blows of overstimulation.

“These kids are not breaking down in school because their parents are doing a bad job or because they are bad kids. Their brains are wired differently.”

PHOTO: ELENA ZHUKOVA

“First, I encourage parents to get an occupational therapist,” recommends Marco, “to help them figure out both at home and at school what environmental changes need to be done to make their lives quiet and consistent. Because it’s the novel stuff that unseats them.” At home, that can be as simple as organizing their room. At school, it can mean putting tennis balls on the legs of chairs so they don’t make sudden sounds as kindergarteners squirm.

Some schools are more accommodating than others, and parents may find that out the hard way. Kids might be asked to leave a school, or parents might pull them out. “About 25 percent of the kids in my clinic end up in independent schools,” says Marco. Cal is in a small and very structured early intervention program, offered through the public school system, that has been incredibly effective in helping him understand the expectations of a school environment. Other SPD kids, like Xander and Elias, are schooled at home, either online or by teachers who come to them. Marco’s biggest takeaway on school choice is this: You don’t want your child to have post-traumatic stress from a school environment that can’t accommodate them. “Whether your kid is 3, 12, or 18, you need their self-esteem intact,” she says.

Her treatment plan also calls for a healthy diet free of simple sugars and simple carbs, a regular bedtime, and consistent exercise, all of which help control the arousal levels of kids – and parents. “If parents are out of control, their kids will be. As a simple start, I suggest they take 10 deep breaths if their kids start to escalate.”

▶ **BRAIN TRAINING:** Typically, kids with SPD have weekly occupational therapy sessions that focus on gross motor skills, as well as fine motor skills for those with dysgraphia.

Elysa Marco, MD ’00

“It is amazing to me to see how really smart kids with terrible handwriting get crushed by school,” says Marco. “On a short-answer test you may know volumes but fail because writing a single sentence is torture.”

Programs that work on cognitive control or attention are also critical for SPD kids who have ADHD in addition. Marco has partnered on this front with Joaquin Anguera, PhD, director of the clinical program at Neuroscape, UCSF’s translational neuroscience center. They are addressing cognitive control deficiencies with a new video gaming platform called Project EVO (developed by Akili Interactive Labs, a UCSF startup). On EVO, kids navigate a character along a winding path, avoiding obstacles and responding to variously colored targets. It’s designed to strengthen the brain’s ability to process and prioritize thoughts and external stimuli, and the game gets harder as a player gets better at it. “Playing EVO actually made a difference in issues of inattention that we measured in the lab and that were reported by parents,” says Anguera, who is also an assistant professor of neurology and psychiatry. “We showed a significant change in the kids’ neural activity. These changes were really deep, and they persisted for nine months beyond the eight-week intervention.”

Though medication is the therapy of last resort, it can be crucial. Marco prescribes beta blockers, which dampen kids’ reactivity, particularly to touch. It’s been a game-changer for Xander. “It has really helped,” he says. “I don’t feel nearly as

PHOTO: GABRIELA HASBUN

When Cal (with his mom, Jennifer) first moved to the suburbs from the city, "he was in sensory overload," she says. The treatment framework for SPD developed by UCSF neurologist Elysa Marco is helping parents control their children's arousal levels.

much pain if someone hugs me. But I'll still never be a huggy person." Judy is thrilled. "I remember Xander saying when he was little, 'I wish I could get a jacket, like a bubble jacket, because then I could just walk around and people could hug or brush up against me and it wouldn't hurt.' Well, with this drug, he's finally found that layer of protection."

▶ **NEW THERAPEUTIC TARGETS:** Anguera and Marco are currently doing a feasibility study of Neuroscape's Body-Brain Trainer (BBT), a video game for kids with ADHD, some of whom also have SPD. To play BBT, kids are hooked up to a heart monitor and put in front of a large-screen TV. They're then directed to touch an image that flashes onto the screen. "We designed BBT to see if cognitive and physical training lead to synergistic effects on cognition, so that one plus one equals seven with respect to cognitive control abilities," explains Anguera. They hope this will be the case for kids with SPD who struggle with attention issues.

Marco is also poised to publish a study with Elliott Sherr, MD, PhD, a fellow pediatric neurologist and resident alumnus. This study looked at whether the genes involved in SPD are the same as or different from those involved in autism; neurogeneticists have uncovered 76 genes that contribute to autism. Marco and Sherr found that kids in Marco's clinic have an enhanced number of changes in these genes. "And so do their parents," adds Marco, who was initially uncomfortable sharing that finding with the parents. But it turned out that few were surprised, given their own life experiences or observations of their spouses'. "We've also found that 18 percent of our kids have an identifiable genetic difference that is distinct from autism," she says.

Knowing SPD's structural, functional, and genetic underpinnings provides Marco and her team with both new therapeutic targets and new ways to measure the success of their therapies. Her goal is to understand the relationship between the differences in SPD kids' brains and their autonomic nervous systems – the part of the nervous system that controls respiration, digestion, the heartbeat, and the fight-or-flight response, which, in SPD kids, can feel like their resting state.

"We've already shown that just eight weeks of training with EVO can change the firing of neurons in the brain," says Marco. "These kids' brains are continually changing through the course of their childhood. If we can keep them in positive environments and train their brains to change in positive ways, we can help them adapt."

With a combination of medication, online schooling, and a deep sensitivity to Xander's needs, Judy has helped him strike a balance between controlling his environment and integrating with society. He is educated at home, at a pace and in a space tailored to his needs, but he interacts with like-minded kids at large, organized meet-ups. He is now gearing up to apply to MIT.

Jennifer and Cindy – also exquisitely attuned to their sons' sensitivities – are still in the thick of it, and their paths forward are less clear. Elias, like Xander, has found great relief from medication that calms his reactivity. He, too, is being taught at home, by teachers who come to him. He still seeks physical solace through near-perpetual motion. "One morning he woke up in a terrible mood," says Cindy. Knowing he needed motion, she handed him a pogo stick and started counting. It took 413 jumps to calm him. Her advice to other parents is this: "The only way you are going to get through is to find other families – I say women, because for me it has been moms – who are going through the same thing. Because there is nothing like having a friendship with somebody who gets it."

Cal is just three and a half and goes to two different schools – one very structured, the other a Montessori school and more experiential. The Montessori kids all know Cal's name, but he doesn't know theirs. They run toward him and he runs away, pretending he's king. It's a game he plays surrounded by other kids, but essentially alone. "We are stuck in the heartbreak of what to expect and what to let go of," says Jennifer. "Will he make friends? Does he want to? Will he be happy?"

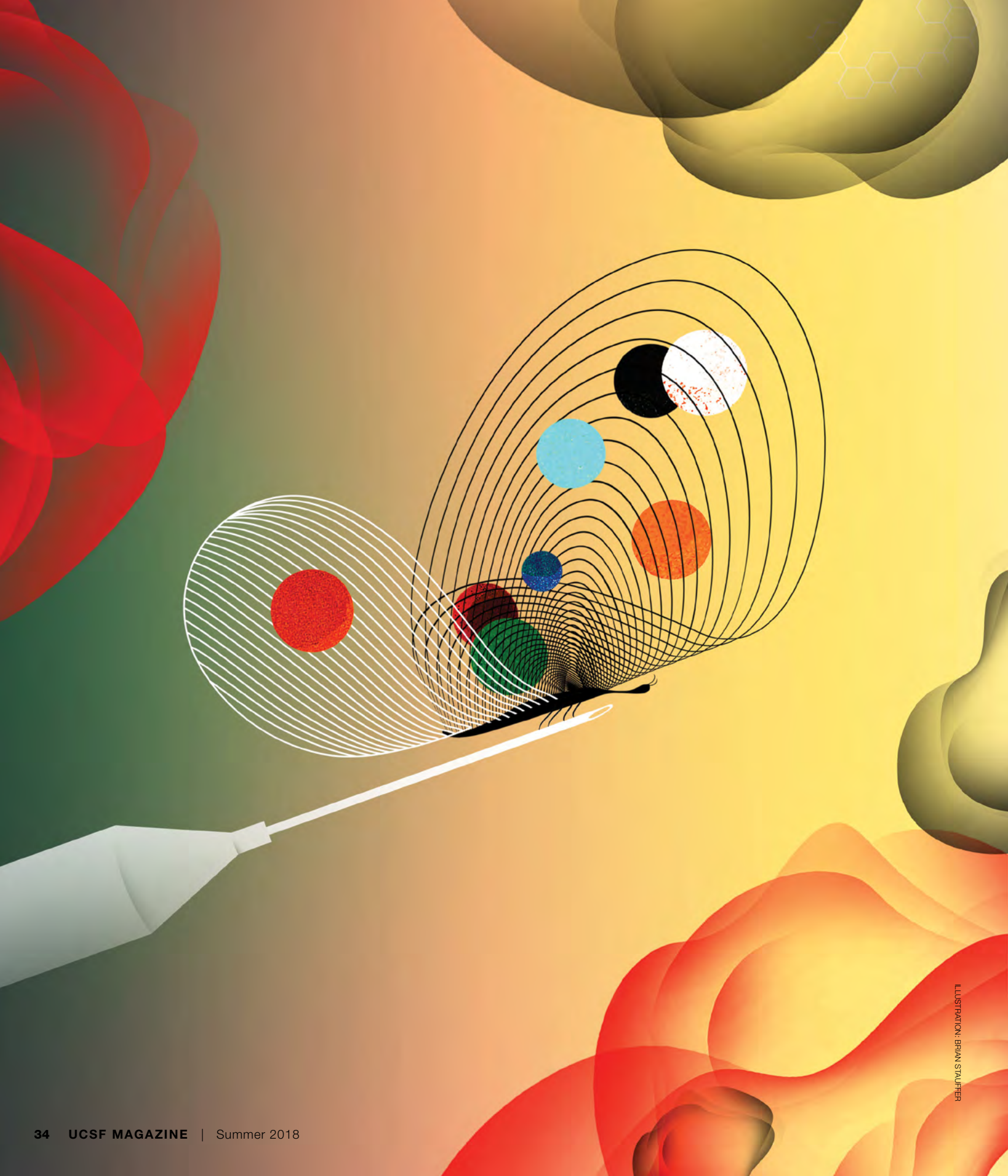
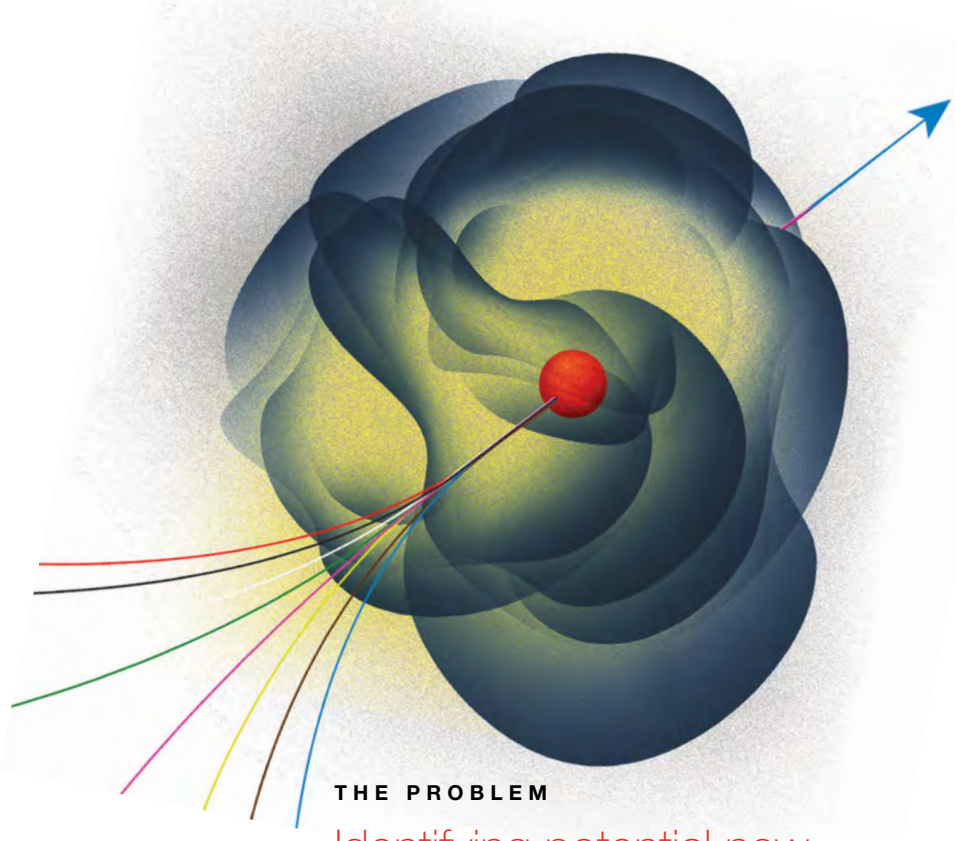


ILLUSTRATION: BRIAN STAUFFER

2018: a drug odyssey

THE EPIC JOURNEY TO BETTER MEDICINES

Take a pill. Get a shot. Use an inhaler. Apply a patch. Fast. Easy. But the journey from discovering and developing effective, precise medications to using them correctly and safely in patients is hardly fast and easy. Nor is it a straight shot. At every step along the way, UCSF School of Pharmacy scientists are challenging the status quo. Their efforts hold the possibility of stunning breakthroughs in how we prevent, treat, and cure disease. Here are some of the most difficult problems they're solving – and how.



THE PROBLEM

Identifying potential new drugs is like trying to hit a target hidden inside a massively complex, constantly moving machine – with a single tiny arrow.

Michelle Arkin,
chemical biologist

Brian Shoichet,
computational chemist

Sourav Bandyopadhyay,
systems biologist

THE SOLUTION

Explore molecular targets in daring new ways.

How can we keep the inner workings of our cells in check?

Inside each of our trillions of cells, thousands of proteins are busy maintaining a stable environment – doing everything from metabolizing nutrients to repairing genetic damage. To convey signals or carry out chemical reactions, these cellular proteins change shape, folding into new configurations that activate other proteins to each do their specific jobs. But sometimes an important protein gets bent into the wrong shape, leading to a cascade of harmful protein-protein interactions – a process that can lead to disease.

Michelle Arkin, PhD, co-director of the Small Molecule Discovery Center, has spent two decades uncovering details of this molecular interplay. By testing millions of molecules – with a particular eye for their influence on protein-protein interactions in test tubes – Arkin seeks to identify promising new drug candidates. She's currently hot on the trail of P97, a protein that's central to interactions which, if they go awry, can cause a variety of conditions, from neurodegenerative diseases to cancers. Illuminating P97's role may lead to new therapies for those conditions.

How can we make drugs side-effect free?

Drugs that treat psychiatric diseases work by influencing neurotransmitter receptors. These are brain proteins – typically found in the spaces, or synapses, between nerve cells – that convey signals from one nerve cell to another. Many psychiatric drugs affect several types of these receptors, meaning they can cause not only the *desired* therapeutic effects, such as the alleviation of anxiety, but also *undesired* side effects, such as insomnia.

Brian Shoichet, PhD '91, is using 3-D models of individual neurotransmitter receptors to design drug-like molecules that fit only into specific receptors – with the aim of alleviating side effects. He and his team recently discovered a highly selective molecule that activates a dopamine receptor subtype called D4. This finding holds promise for the development of medications to treat addiction and psychosis that don't induce the movement disorders commonly associated with many of today's psychiatric drugs.

Can a new point of view turn a drug discovery failure into success?

Decades ago, scientists noticed that cancer cells produce signals that promote tumor growth. They tried blocking some of those signals with a class of drugs known as PI3K inhibitors. The result? Tumors stopped growing – but only in petri dishes and animal models. In clinical trials, the drugs totally failed to extend the lifespans of cancer patients – so PI3K inhibitors were shelved.

Sourav Bandyopadhyay, PhD, wondered how such promising drugs could have stumbled at the finish line. Using a new technology that he developed, he measured the levels of all the different signals present in tumor cells and found that a handful of signals changed in response to PI3K inhibitors, allowing cancer to compensate for the effects of the drugs. Combining PI3K inhibitors with other drugs that block these additional signals led to an even more dramatic decrease in tumor growth in animal models, compared to PI3K inhibitors on their own. He's now exploring ways to test this new combination therapy in clinical trials, making good on the therapeutic promise of one of cancer biology's earliest discoveries.

ILLUSTRATIONS: BRIAN STAUFFER; TOP AND MIDDLE PHOTOS: ELISABETH FALL; BOTTOM PHOTO: ALEXA ROCOURT

THE PROBLEM

Drugs travel through our bloodstreams into every corner of our bodies – both where they're needed and where they're not – and can cause potentially dangerous side effects in healthy tissues or organs.

OUR SOLUTION

Get drugs to exactly where they're needed.

How can we make sure drugs affect only sick cells and not healthy ones?

Chemotherapy drugs attack fast-growing cancer cells, but these drugs are not discerning; they attack fast-growing *healthy* cells, too. Luckily, tiny functional differences separate healthy cells from cancer cells. By finding and exploiting those differences, it may be possible to create molecular machines that set out to find sick cells, infiltrate them, and only then release the drug, thus sparing healthy tissues. Because cancerous cells have abnormal amounts of free-floating iron, **Adam Renslo, PhD**, co-director of the Small Molecule Discovery Center, realized cancer drugs could be improved by inserting them into molecular envelopes that require the presence of iron to open.

Renslo's method lays the groundwork for treatments that reach only cancerous cells, allowing health care providers to use smaller doses of cancer-fighting medicines and still achieve the same therapeutic effect – but with fewer side effects – compared to existing methods of chemotherapy delivery.

How can we design molecules nimble enough to negotiate the body's obstacle course?

Our bodies control which substances can enter our tissues, whether the destination is an organ like the brain or a specific type of cell. When designing a potential new drug for a given disease, scientists must ensure that it is physically capable of both penetrating the body's defenses and being accepted by its target once it arrives. **Matthew Jacobson, PhD**, is working to overcome this challenge using novel molecules called peptide macrocycles, which are capable of penetrating the biological membranes that separate tissues and cells. For all their girth, macrocycles are especially nimble.

Jacobson's approach involves engineering small "hinges" into macrocycles, allowing them to fold into specific shapes to pass through the body's various barriers. He's shown how tweaks to a class of these molecules can be used not only to ensure their passage through the gut and into the bloodstream, but also to improve their ability to inhibit a certain receptor, called CXCR7, that plays important roles in the development of heart disease and cancer.

How can we pinpoint and control drug delivery over time?

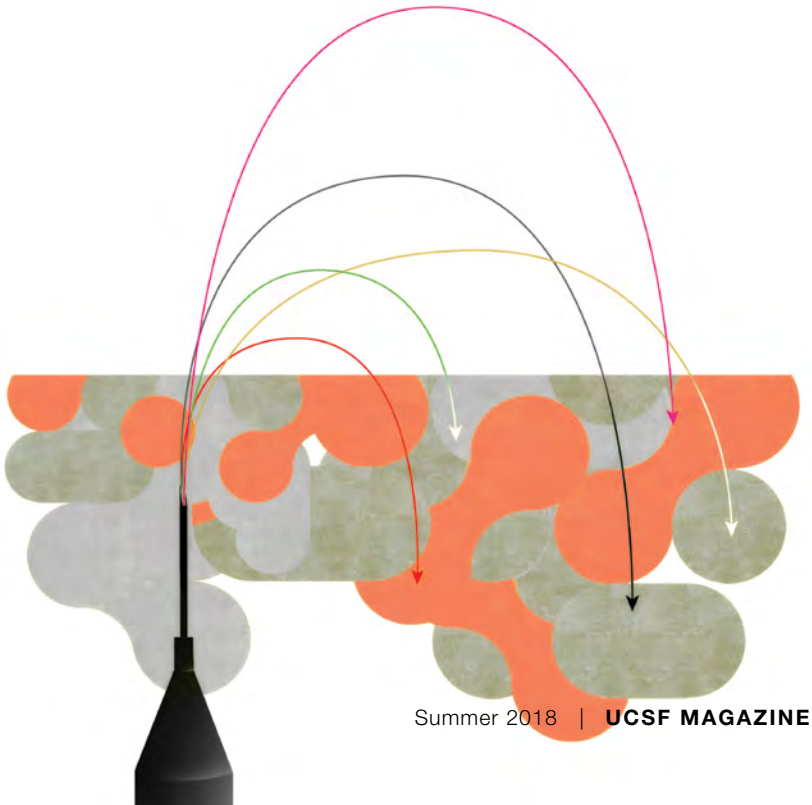
A good drug is less than ideal if it's hard to use. Nanotechnology-based drug delivery vehicles, placed inside the body, can eliminate the need for patients to administer drugs themselves on a tight schedule. These vehicles can also deliver drugs continuously, maximizing their effectiveness. Anti-glaucoma drugs are a case in point. Glaucoma is currently treated using liquid drops that reduce pressure in the eye, but elderly patients struggle to administer the drops correctly and on the right schedule.

Tejal Desai, PhD '98, has engineered a tiny implant that slowly releases a controlled amount of the pressure-reducing drug – from within the eye – sparing glaucoma patients from daily eye-drop regimens. And she's applying the same concept to the prevention and treatment of HIV/AIDS as well. Compared to men, women experience a higher risk of contracting the HIV virus if they miss taking

Adam Renslo, medicinal chemist

Matthew Jacobson, physical chemist and MacWilliam Distinguished Professor

Tejal Desai, bioengineer and Ernest L. Prien Professor



TOP AND MIDDLE PHOTOS: ELISABETH FALL; BOTTOM PHOTO: STEVE BABULJAK

their preventive medications. The Desai lab is creating a biodegradable drug delivery device, that's inserted under the skin, to solve this problem. This may help arrest the spread of HIV globally, especially among women.

THE PROBLEM

How we live varies as much as our biological makeups; both affect the outcome of drug therapies.

OUR SOLUTION

Take into account all the factors that can influence a drug's effectiveness for each individual – from genetic heritage and lifestyle to age and weight.

Jennifer Cocohoba, clinical scientist and pharmacist

Rada Savic, pharmacometrician

Esteban Burchard, physician-scientist and Hind Distinguished Professor

How can we treat chronic pain without fueling opioid addiction in women living with HIV?

As the pharmacist for the UCSF Women's HIV Program, **Jennifer Cocohoba, PharmD '01**, creates and monitors individualized drug treatment regimens for her HIV-positive patients, many of whom have been affected by traumatic life experiences such as homelessness, drug addiction, sexual assault, or physical abuse. They're at high risk of developing chronic pain, both because of these traumas and because of the painful conditions – like neuropathy or avascular necrosis – caused by HIV or the drugs used to treat it.

Alarmed by these facts, and by the rising national incidence of prescription painkiller overdoses in women, Cocohoba and her UCSF School of Nursing colleague Yvette Cuca Bromberger, PhD '13, MPH, set out to learn more about these patients and their relationships to opioids. They're asking patients about their dependence on opioids, perceptions of the drugs' risks, and attempts to reduce their opioid use. Armed with initial research data, they hope to then design and test interventions to promote safe use of opioids for effective pain relief, especially for women living with HIV.

How can we use existing TB medications more effectively in individual patients worldwide?

Tuberculosis (TB) is curable and preventable, according to the World Health Organization. But it still kills nearly 2 million people a year, making it the deadliest infectious disease in the world. **Rada Savic, PhD**, thinks those deaths are unnecessary – and she knows how to prevent them. For decades, health care providers have treated TB using a standard six-month regimen of a handful of antibiotics, but Savic's research has shown that this one-size-fits-all approach doesn't work for all patients. Those who need treatment for less than the standard six months often end up bedridden for a few extra months due to side effects. And those who need treatment for more than six months can end up with recurring bouts of infection, which are more likely to be drug resistant – and deadly.

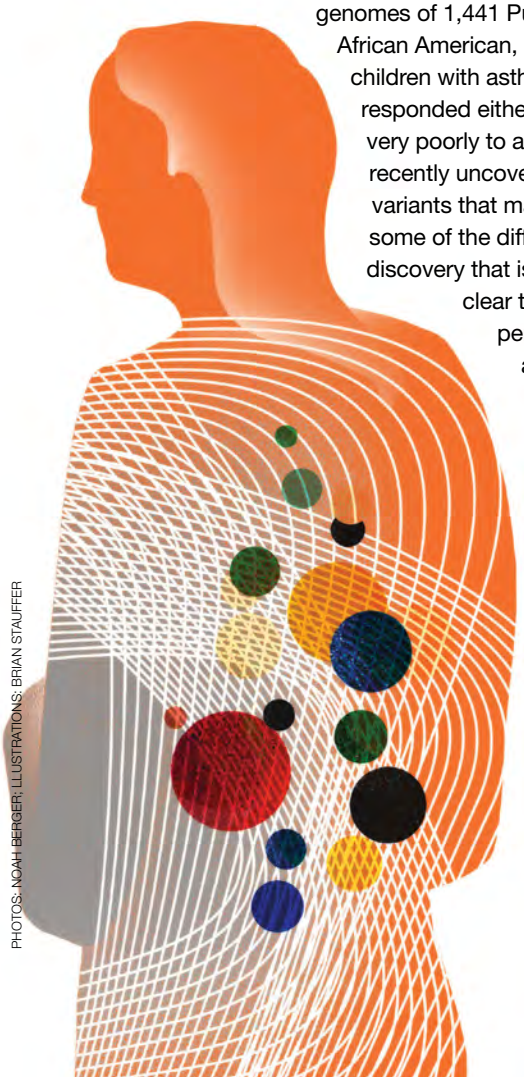
Based on patient data already collected by clinics worldwide – like X-rays, bacterial culture results, age, and nutrition status – Savic is confident that health care providers can successfully implement an evidence-based treatment plan for every patient, tailoring medication dose and frequency to each individual case. She's optimistic that by following this course, the world may soon eradicate TB, once and for all.

TOP PHOTO: NOAH BERGER; MIDDLE PHOTO: ELISABETH FALL; BOTTOM PHOTO: STEVE BABULJAK

How can we leverage the unique genetic ancestry of each individual to better treat patients with asthma?

Variations in our genetic ancestry, as well as in the social and environmental factors we're exposed to, can affect how vulnerable we are to disease. Our genetic ancestry can also influence the safety and effectiveness of drugs we're prescribed. This is shockingly true of asthma – the most common chronic disease in children in the U.S. – and the medications used to treat it.

For the past 20 years, **Esteban Burchard, MD, MPH**, has been studying the causes of health disparities in children with asthma, focusing on Latino and African American children. In the U.S., Puerto Ricans and African Americans are three times more likely to die from asthma than Mexicans and non-Latino whites. In addition, they have the lowest response to albuterol, the most commonly prescribed asthma medication worldwide. Burchard, together with his School of Pharmacy colleagues Ryan Hernandez, PhD, and Nadav Ahituv, PhD, plus 12 other research teams from eight universities, set out to uncover why there are racial/ethnic differences in patients' responses to albuterol. The group investigated the entire genomes of 1,441 Puerto Rican, African American, and Mexican children with asthma who responded either very well or very poorly to albuterol. They recently uncovered genetic variants that may explain some of the differences, a discovery that is helping to clear the path to personalizing asthma treatments for minority children.



PHOTOS: NOAH BERGER; ILLUSTRATIONS: BRIAN STAUFFER

THE PROBLEM

Policy makers, awash with complex new medical information, face daunting challenges.

OUR SOLUTION

Provide them with evidence-based recommendations that prioritize patient health, safety, and access to treatments and diagnostic tests.

How can we better advance, approve, and monitor medical products?

The development and ultimate approval of new drugs – and the monitoring of drugs after they're on pharmacy shelves – involve intense scrutiny and regulation by the U.S. Food and Drug Administration (FDA). This is necessary to ensure that medications are safe and effective. Developing the rules and tools to do this is a science in itself – a science that **Kathy Giacomini, PhD**, aims to improve as co-director of the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation (CERSI).

Giacomini is now leading a major research study looking at 400 of the many inactive ingredients in generic tablets, capsules, and syrups taken orally – ingredients such as coatings, binding agents, and thickeners – that, with the active ingredients, travel to patients' intestines. There, the active ingredient is absorbed into the bloodstream by intestinal transporters. Do the inactive ingredients, which can make up 90 percent of a drug formulation, hinder how well their active companions are absorbed? She intends to find out. Her results may help the FDA better regulate any inactive ingredients that hinder absorption and ensure that generic drugs used by patients have equivalent biological effects, dose by dose, to their brand-name counterparts.

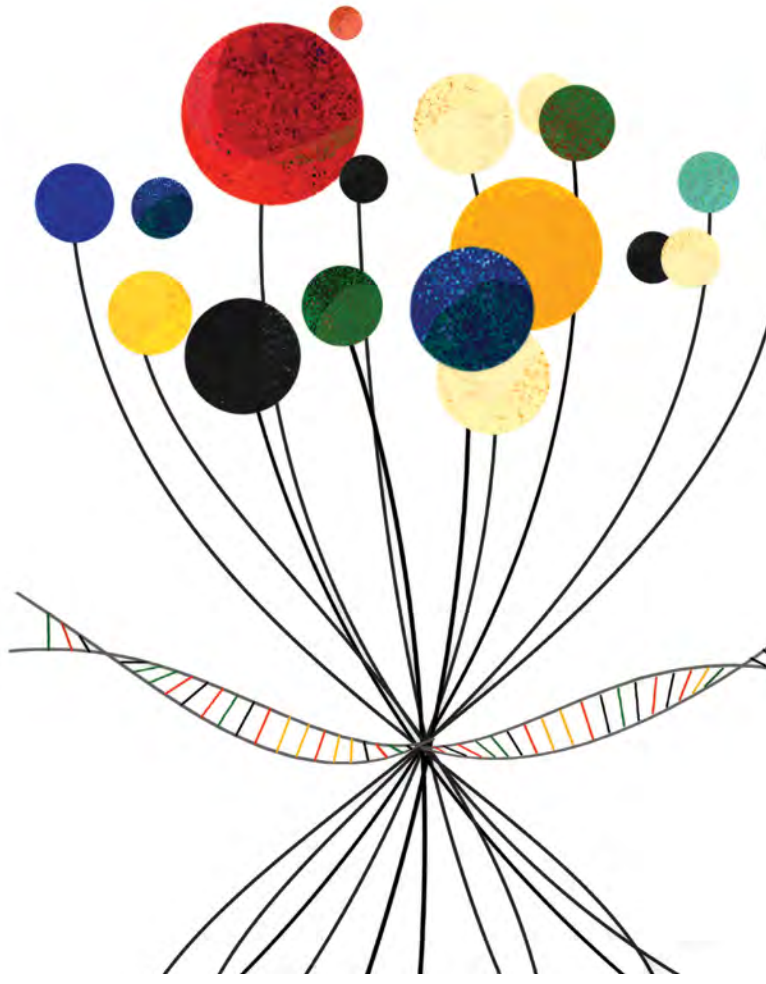
Kathy Giacomini, regulatory scientist and pharmacogenomicist

Kathryn Phillips, health services and policy researcher

How can we drive health policy so that genetic testing and the information it reveals benefit patients?

Genetic tests on the market today hold the promise of health care tailored to each patient's unique biology and

situation. But **Kathryn Phillips, PhD**, knows there's a wide gap between this promise and a patient's ability to benefit from it. She's methodically narrowing that gap by asking hard questions and revealing critical answers, in her role as director of the Center for Translational and Policy Research on Personalized Medicine (TRANSPERS). Her team there recently found that the use of, and insurance coverage for, genomic tests for developmental disabilities such as autism, vary greatly. Instead of benefiting from diagnoses based on genomic testing, many of the one in six children in the U.S. who are developmentally disabled end up on diagnostic odysseys lasting many years. Findings like this – which Phillips and her fellow TRANSPERS researchers then share with policymakers – are essential if personalized medicine is to benefit all patients equitably.



THE PROBLEM

It takes too long to get effective new treatments to patients.

OUR SOLUTION

Start incrementally and locally – then apply the best solutions broadly.

Marilyn Stebbins, clinical scientist and pharmacist

Lisa Kroon, clinical scientist and Thomas A. Oliver Professor

How can we keep patients from being readmitted to the hospital because of medication problems?

Not paying strict attention to your medications can have serious, even deadly, consequences. It's estimated that one million emergency department visits and 125,000 hospital admissions are caused each year by medication issues (called adverse drug events) in outpatient settings. **Marilyn Stebbins, PharmD '88**, is determined to change those statistics, beginning with patients who are transitioning from the hospital to home.

In collaboration with UCSF Medical Center and Walgreens at UCSF, Stebbins recently launched what's known as a meds-to-beds program – a voluntary research pilot program that delivers medications to a patient's hospital bedside as part of the discharge process, then follows up with patients about their medications, post-discharge, via an automated phone call. Any answer by the patient to the automated call triggers a personal follow-up call by a nurse, or by a pharmacist if the call involves a medication problem.

While all discharged patients receive the phone call, the meds-to-beds patients also leave the hospital with their prescribed medications in hand. The results to date? All meds-to-beds patients studied transitioned to home with their medications and were taking their medications, as prescribed, once they were home. Stebbins plans next to look at readmission rates for these patients and determine whether the program has an impact on medication-related readmissions.

Can pharmacists expand how they serve patients' medication needs?

Since 2013, state laws have begun empowering specially trained, licensed California pharmacists to practice as legally recognized health care providers. They can now order tests to monitor the safety and effectiveness of medications, and they can prescribe hormonal contraception, nicotine replacement therapy, travel medicines, and naloxone (which can reverse the effects of an opioid overdose). A subset of pharmacists, known as advanced practice pharmacists, can now also initiate, adjust, or discontinue medication therapy for patients, joining their pharmacist peers who've been practicing at this level for years under special physician practice agreements in health care facilities.

TOP PHOTO: ELISABETH FALL; BOTTOM PHOTO: NOAH BERGER

Lisa Kroon, PharmD and resident alumna, was instrumental in implementing these laws, and she has now turned to researching their impact on patient care. Preliminary results of a recent study, which she led in partnership with the national Albertsons pharmacy chain, indicate that community pharmacists can serve as convenient access points for patients seeking hormonal contraception. The next step? Research to explore whether such access can help lower the incidence of unintended pregnancies. Her findings are shedding light on the impact of expanding pharmacist practice authority across the nation.

How can we make sure we have the medications patients need in our hospitals and clinics?

If you're admitted to a hospital, the idea that the institution might run short of a medication you need – an antibiotic, a painkiller, an anesthetic – would probably not cross your mind. But since 2005, the number of drug shortages in the U.S. has quadrupled – in many cases impacting patient care, health outcomes, and costs. It's a national issue that's generally addressed with a short-term approach, by reacting to shortages rather than anticipating them.

As director of the Medication Outcomes Center, **Rosa Rodriguez-Monguio, PhD**, is leading a collaborative research agenda – involving experts in pharmacy, medicine, health economics, informatics, policy, and precision medicine – to ensure safe, cost-effective, equitable, evidence-based medication use at UCSF Health. Her current study aims to unearth the root causes and effects of drug shortages. With these findings in hand, she then plans to develop a forecasting model for anticipating and preventing potential drug shortages long before they arise, a model she hopes could ultimately be applied across all UC health care settings.

How can we protect the public against poisonings?

Poisons are everywhere, from chemicals under the kitchen sink to toxic smoke in the air. Two million children, most of them under age 6, will swallow a poison this year in the U.S.

The statewide California Poison Control System (CPCS), administered by the School of Pharmacy, keeps busy responding to calls from the public and health care providers about exposures to poisons and actual poisonings. CPCS poisoning specialists provide free, expert treatment advice and referrals 24/7, every day, at 800-222-1222 – handling 250,000 calls each year. Fifty-one percent of these calls concern children.

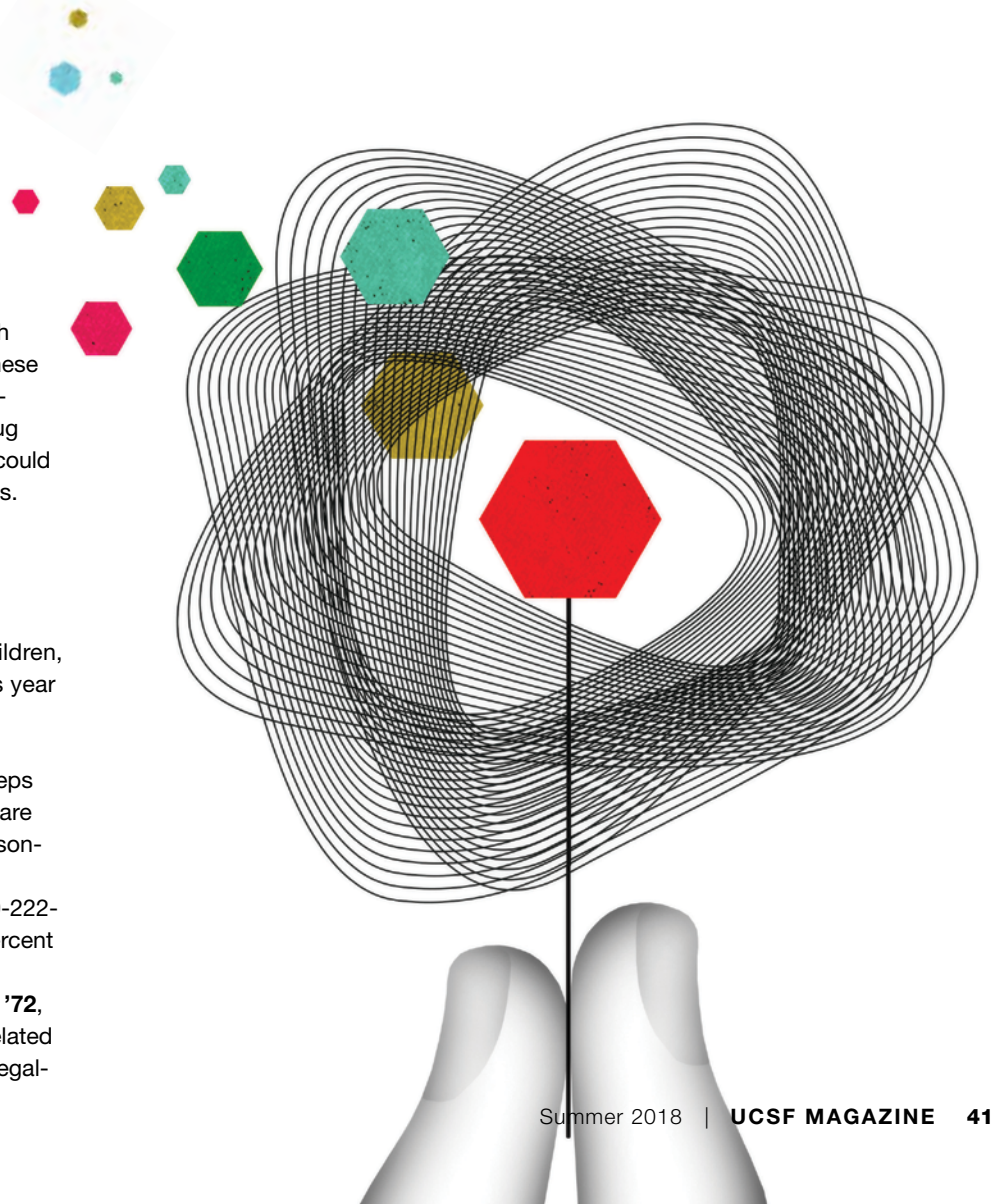
CPCS Executive Director **Stuart Heard, PharmD '72**, and his team are currently fielding an uptick in calls related to unintentional pediatric marijuana exposure due to legalization increasing the availability of marijuana edibles, such as cookies and candies. A recent exposure at a child's birthday party in San Francisco brought 12 children and 9 adults to emergency departments, all with central nervous system effects and many with cardiovascular effects from inadvertently eating gummy candies laced with THC, the psychoactive ingredient in cannabis. Follow-up research by the CPCS concluded that health care providers should consider exposure to THC in children who show altered mental states and should test for it when there is probable cause.

As the CPCS continues to provide Californians with around-the-clock treatment advice in cases of exposure to poisons, the results of CPCS studies like this are also keeping health care procedures and policies in synch with emerging sources of potential poisonings.

Contributors: Grant Burningham; Levi Gadye, PhD; Paula Joyce; and Susan Levings

Rosa Rodriguez-Monguio, health economist

Stuart Heard, pharmacist and health services and policy researcher



PHOTOS: NOAH BERGER; ILLUSTRATIONS: BRIAN STAUFFER

Who Are Mapping New Terrain to Navigate New Ways out of Disease

THE VISIONARIES

Through side-by-side comparison of typical versus genetically altered brain development in frogs, Helen Willsey's work could reveal where, how, and when autism sets in so it can be stopped before it starts.

Helen Willsey, PhD, and Bo Huang, PhD, are next-gen cartographers. Each charts infinitesimal territory to reveal the mechanics of disease. Willsey's and Huang's work perfectly exemplifies "Decoding Life to Improve Health," one of the three grand challenges targeted by **UCSF: The Campaign**.

Willsey's frontier is the brain. She's a member of the Psychiatric Cell Mapping Initiative, which seeks to chart the function of genes involved in every psychiatric disorder – starting with autism – so we can understand mental health on a molecular level.

A postdoctoral scholar and member of the UCSF Weill Institute for Neurosciences, Willsey devised the perfect model of autism in a frog and now tests how and where genes associated with autism affect the developing brain. She chose to study frogs because she can genetically alter just one side of a frog brain while leaving the other side untouched as a control.

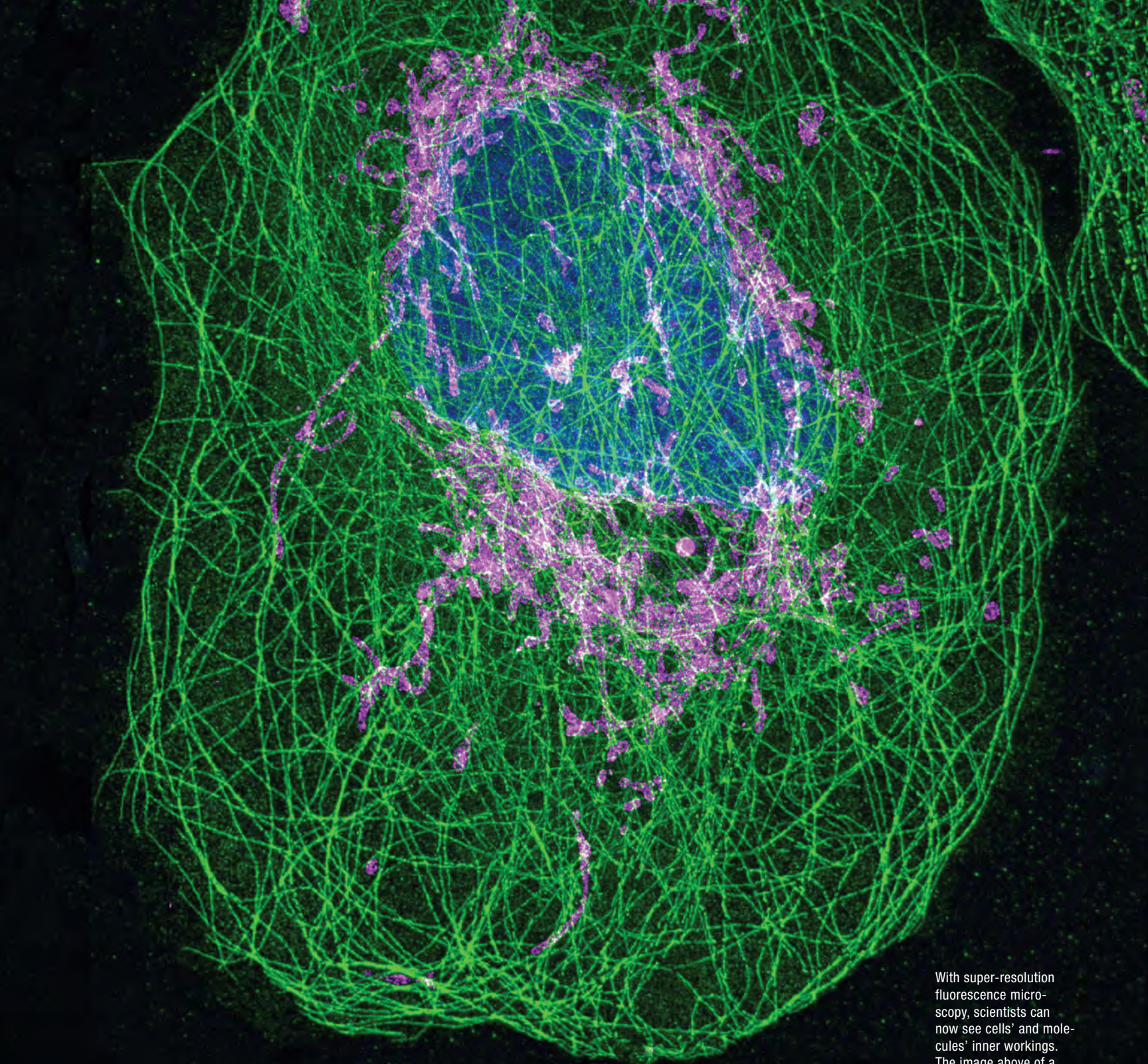
Huang's universe is vastly larger. He studies the human proteome, which consists of all the proteins expressed by a genome, cell, tissue, or organism. As an investigator with the Chan Zuckerberg Biohub, he is part of an effort to label each and every protein produced by a human gene and to track its function.

Huang, who is also a professor of pharmaceutical chemistry and this year's recipient of the Byers Award in Basic Science, decodes life by building better microscopes. He pioneered the development and application of super-resolution fluorescence microscopy, which enabled humankind to visualize overall cell function and the dynamics of the molecules within the cell. He recently rocked the field by tagging the DNA within genes using the CRISPR gene editing tool, so that scientists can now identify and track genes' specific function with fluorescence microscopy.

Fresh tracks, new territory, boundless potential.

CAMPAIGN.UCSF.EDU

IMAGE: WILLSEY LAB



With super-resolution fluorescence microscopy, scientists can now see cells' and molecules' inner workings. The image above of a HeLa cell reveals its mitochondria, or cellular powerhouse, and its microtubules (in green), or structural support. The powerful tool, pioneered by Bo Huang, is helping scientists gain a clearer understanding of the processes that underlie disease.

IMAGE: HUANG LAB

ALUMNI HUB

Welcome to your world

Looking for an easy way to keep up with UCSF, your school, and your alumni friends?

Go to **alumni.ucsf.edu**, our all-new UCSF Alumni Relations website. The site makes it easy to find the latest news, career services, and learning opportunities. It features a calendar of upcoming alumni events and stories that, like the profiles in this issue's Alumni Hub, give you a window into the lives of your fellow alumni.

From the new site, you can easily link to **UCSF: The Campaign**, where you will find more about the most recent accomplishments of our faculty and students in their search for radical solutions to today's health challenges. There are also quick links to UCSF.edu, UCSF's public website, and UCSF Connect, our social platform for alumni, students, residents, fellows, and postdocs. Haven't signed up yet? Join nearly 1,900 followers at **ucsfconnect.com** or **alumni.ucsf.edu**.

One URL is all you need to remember! Check it out today at

alumni.ucsf.edu

SCHOOL OF NURSING

Catherine Gilliss, RN, PhD '83

Birthplace: Stamford, Conn.

Now: San Francisco

Position: Dean and Styles Professor of Nursing, UCSF School of Nursing, and Associate Vice Chancellor for Nursing Affairs, UCSF

Hobbies: Playing the piano, spending time with her five grandchildren

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Former department chair Catherine Gilliss returned to UCSF last fall as dean, her third deanship at a top U.S. nursing school. Here's what the nationally recognized expert in family nursing has to say about where the profession is going and how UCSF will help it get there.

You have achieved an academic nursing three-peat, serving as dean at Yale, Duke, and now UCSF. What do you love about being dean?

My friends are calling me Dean Again, but philosophically, the attraction is about giving back to the place that launched my professional life. Coming back to UCSF after 20 years, I feel like I'm returning home. And I like working. I find being a dean satisfying because I'm fascinated by complex organizations, and I'm quite committed to reform. I have always chosen to be where change was expected; that has been true throughout my career.

Over your five decades in nursing, how has the field evolved?

Nursing has always been about helping people get what they need to be healthy – both care and information. That has not changed, but the *practice* of nursing has changed dramatically. There's a much faster pace of progress in the science that underlies care and the technology that's used to deliver it. For instance, our partners at the VA [San Francisco Veterans Affairs Medical Center] tell me they now expect their registered

nurses not only to be technically competent at bedside, but also to understand population health care. At UCSF, we want to ensure that we are preparing our graduates with the skills needed for today *and* tomorrow.

> **"My friends are calling me Dean Again, but philosophically, the attraction is about giving back to the place that launched my professional life."**
>
> *– Catherine Gilliss, RN, PhD '83*

What is your vision for the School of Nursing?
UCSF has always been a leader in science and education for clinical care. I expect that we will increase our use of technology in delivering educational programs and provide more opportunities for our students to use technologies, such as telehealth, for monitoring and delivering care. With the opening of our Center for Physiologic Research, I also envision that we will advance the science of health monitoring, using new instrumentation and large data sets to better understand patterns of health and illness.

What other opportunities does technology present?
Most of our students are licensed as registered nurses, and many of them are working. We have to develop easier access to our educational programs for the working student. One possibility is online offerings: Many other schools have moved toward that, even for high-touch programs. We also have the opportunity to repurpose elements of our degree offerings for high-quality continuing education for working health professionals, who must engage in lifelong learning to stay current.

Do you think of yourself as a nurse or a leader?
Both. I spent 2015 as a fellow at Stanford's Distinguished Careers Institute and was planning to study leadership but moved in a different direction. I turned toward courses that refreshed old interests – one in writing memoirs and another in American song. The experience reminded me that I was a nurse – and more. Nursing has been at my core for a long, long time. And I love creating, organizing, enabling, reforming. I hope to be remembered for those qualities.

PHOTO: ELISABETH FALL

Bijan Boldajipour is on the fast track at Kite Pharma, a subsidiary of Gilead, where he oversees the development of cancer-targeting cell therapies that can fight – and perhaps someday cure – leukemia and other cancers.

How did you get interested in molecular biology?
I had biology and chemistry teachers who really inspired me. When I graduated from high school, I saw a flyer advertising a new, prestigious graduate program at the University of Göttingen that really excited me. I needed a bachelor's program before I could go there, so I joined one that focused on life sciences research. I tend to like what comes easy to me, and after that, everything came easy. I ended up joining that graduate program for my master's and PhD.

How does cell therapy work?
We take immune cells from patients, genetically engineer them, then reintroduce them back into the patients. The primary applications are lymphomas and leukemias, and the success rates are so high that oncologists are talking about cures. It's a complicated drug, incredibly potent, so only select academic health centers have access to it for now, and clinicians need special training to detect its side effects.

What's most rewarding about what you do?
A lot of labs are working on this, so the field is competitive and timelines are very fast. Novartis and Kite both started their clinical trials in 2012 and had approvals by 2017. It's really satisfying for the scientists working on these drugs to see them approved so quickly. The multiple myeloma drug I developed at Pfizer before joining Kite is not yet in the clinic, but the prospect of seeing it in use in just a few years, and hopefully benefiting patients, is very powerful.

What do you like most about San Francisco?
Germany is a rule-dominated country. San Francisco has more freedom, and no one tells you how to live your life. My husband and I live in the Castro, and it's always exciting; you see things you'd never see anywhere else. My parents came to visit and they said, "Oh, there's a naked person! Is that allowed?"

Bijan Boldajipour, PhD, Postdoc Alumnus

Birthplace: Bremen, Germany
Now: San Francisco
Position: Director, Technology Development, Kite Pharma
Hobbies: Working out, socializing, traveling

GRADUATE DIVISION

SCHOOL OF PHARMACY

Jake Beverage, PharmD '08

Birthplace: Baltimore, Md.
Now: San Diego, Calif.
Position: Co-founder and CEO, Sirenas, LLC
Hobbies: Surfing, being in nature, spending time with his family

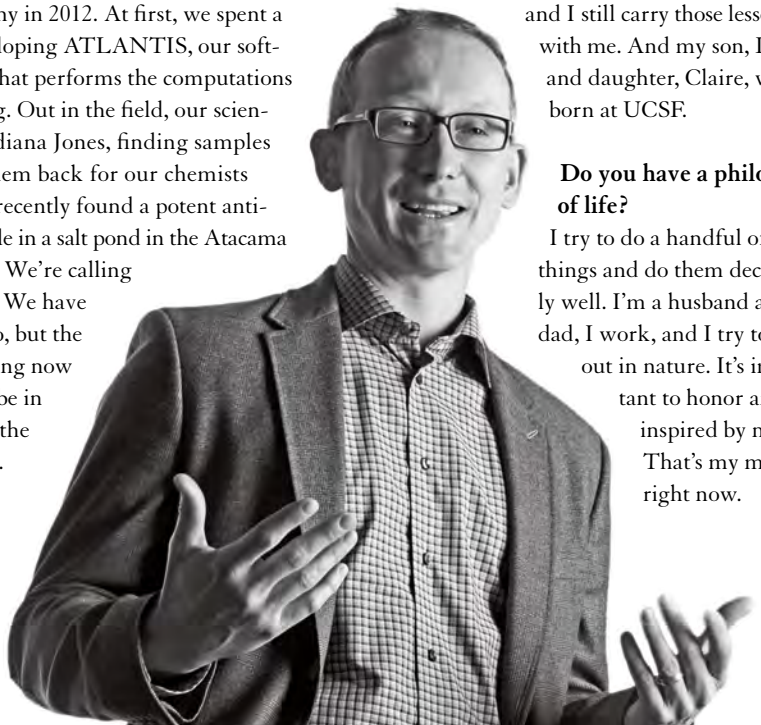
Jake Beverage combines his curiosity about biology with his passion for nature at drug development startup Sirenas. He calls it "interrogating chemistry," using computational approaches to mine nature for medicinal insights that no scientist could ever have imagined.

When did you first get interested in pharmacy?
I've always been fascinated with medicine, pharmacology, and the idea that chemistry can influence physiology. My view of medicine is very pragmatic: The idea of having to take a pill once a week instead of three times a day really matters to me.

How did you land at Sirenas?
I met my co-founder Ed [Esquenazi] at Vanderbilt 20 years ago. We studied biology together and have been talking about science ever since. He actually taught me to surf. He also studied oceanography and got the idea to start the company in 2012. At first, we spent a lot of time developing ATLANTIS, our software platform that performs the computations and data mining. Out in the field, our scientists are like Indiana Jones, finding samples and shipping them back for our chemists to analyze. We recently found a potent antimalarial molecule in a salt pond in the Atacama Desert in Chile. We're calling it Atacamazole. We have a long way to go, but the stuff we're finding now has a chance to be in clinical trials in the next three years.

What was most valuable about your UCSF experience?
I think of UCSF as a shining tower of knowledge and collaboration between the basic and clinical sciences. The whole last year of my training was clinical rotations, seeing patients, and I still carry those lessons with me. And my son, Luke, and daughter, Claire, were born at UCSF.

Do you have a philosophy of life?
I try to do a handful of things and do them decently well. I'm a husband and a dad, I work, and I try to get out in nature. It's important to honor and be inspired by nature. That's my mantra right now.



PHOTOS: STEVE BABULJAK, MICHAEL BALDERAS

Marilyn Wong started medical school in her thirties to bring her special blend of cultural sensitivity and population medicine to her patients. Now retired, she continues to pass on her wisdom to students in the Bay Area and beyond.

What have been your deepest influences?
We came to San Francisco when I was 11, and my grandparents lived on Grant Avenue. My first impression was that Chinatown looked so dilapidated. That was my impetus for studying architecture at UC Berkeley, but I dropped out at the height of the student movement in the '60s, which influenced me greatly. In medicine, I was always interested in social determinants of health and all those factors that influence a person's well-being.

What inspired you to go to medical school?
I worked at a community center in Chinatown and helped people as an advocate and interpreter. I got involved taking patients to the hospital and became interested in medicine. I was 31, with two young daughters, not even a science major, but UCSF took a chance on me.

Do you have a pet project?
About 10 years ago, I was looking for retirement projects and was shocked that UC Berkeley didn't have a single class on Asian American health. We started the Asian American Pacific Islander Health Research Group, and now many of my former students are working in medicine, nursing, social work, and other fields. They form lifelong friendships, and I get to see them blossom. Now, as a member of the UCSF Medical Alumni Association board, I'm hosting walks for first-year students through Chinatown, whose residents will be some of their future patients. I hope other alumni will lead similar tours through neighborhoods like the Tenderloin, the Mission District, or Hunters Point.

What are you most proud of?
My husband and I both took nontraditional paths through life, and his support has been critical to everything I've done. I also appreciate the meaningful lives my two grown daughters and their spouses are leading, and I'm the proud grandmother of their four children.

Marilyn Wong, MD '86, MPH

Birthplace: Hong Kong

Now: Berkeley, Calif.

Position: Retired physician and volunteer

Hobbies: Spending time with her family, making paper collages, gardening

SCHOOL OF MEDICINE

SCHOOL OF DENTISTRY

David Johnson, DDS '82, Postgraduate Certificate in Orthodontics '84

Birthplace: San Mateo, Calif.

Now: Alameda, Calif.

Position: Owner, Johnson & Jolley Orthodontics (with Loren Jolley, DDS '03, MS '06); immediate past president, UCSF Orthodontic Alumni Association

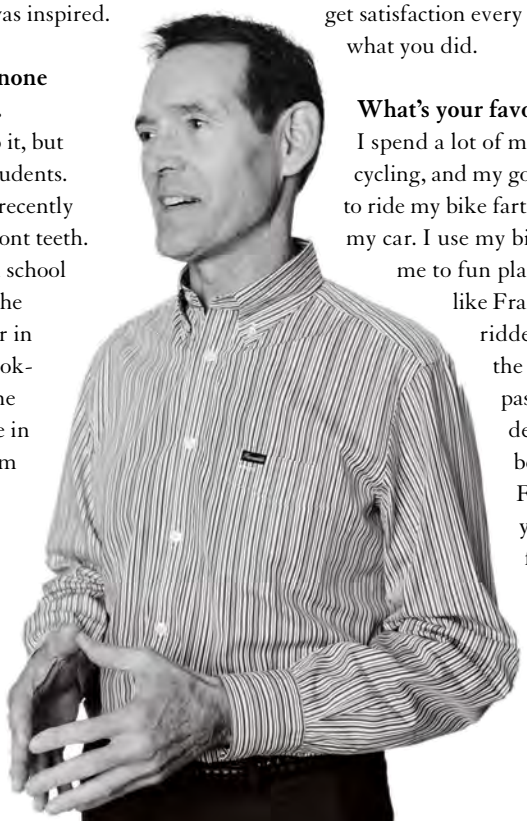
Hobbies: Cycling, traveling, skiing, winemaking, iPhone-ography

Dave Johnson got his education *and* his braces at UCSF. Now, he puts smiles on kids' faces and is an ambassador for the profession, training and even finding jobs for a new generation of orthodontists.

How did you get such perfect teeth?
Our family dentist [Douglas Clemetson, DDS '68] told me, "You should be a dentist and you should go to UCSF." There was no way my single mom could afford braces for us. So, when I arrived here, I wandered down to orthodontics and said, "I'm going to be a dentist, and I've got really crooked teeth." They said, "Get in the chair." I saw what orthodontists could do, and I was inspired.

You seem disappointed that none of your kids became dentists.
I couldn't talk any of them into it, but I've encouraged patients and students. One patient I treated at age 13 recently came in for a tune-up on her front teeth. She said she had gone to dental school because I encouraged her, but she hadn't found a job yet. I put her in touch with a friend who was looking for an associate, and now she works down the street from me in Alameda. That gives me a warm spot in my heart.

What's the best part of orthodontics?
It's the perfect mix of art and science. It takes science to move teeth, but it takes art to know where to put them. Just yesterday, we took off three sets of braces, and those are new smiles we've released into the world. You get satisfaction every day from seeing what you did.



What's your favorite hobby?
I spend a lot of my free time cycling, and my goal every year is to ride my bike farther than I drive my car. I use my biking to take me to fun places in Europe, like France, where I've ridden almost all the mountain passes of the Tour de France. The best thing about France is that you get to eat the food guilt-free after an all-day bike ride that burns 5,000 calories.

PHOTOS: SONYA YRUEL

PHOTO: LOREEN ATALLAH

Llamarama...

Llamapalooza... No-Drama Llamas... Call it what you will, but the March 12 visit by these sociable quadrupeds to the Mission Bay campus was a hit with midterm-stressed students and others seeking a brief respite from their busy day. Why llamas, you may ask? As the *New York Times* put it, "Look at a llama and it'll gaze back sympathetically ... looking for all the world like it understands you and really cares about your problems." The llama visit was organized by the UCSF Graduate and Professional Student Association.

UCSF The Campaign

"When I started this work, well-meaning individuals told me, 'Dayna, you're not going to solve poverty.' My answer is always, 'Well, we certainly have to try.'"

YOUR COMPASSION HER RESOLVE

Throughout her 20-year career at UCSF Benioff Children's Hospital Oakland, pediatrician Dayna Long, MD, has clearly seen how issues ranging from homelessness to food insecurity affect her patients' health. So she spearheaded a program that links families with community resources, giving countless kids a better shot at a healthy childhood. **With every gift to UCSF, you support the resolve of people like Long to disrupt poverty.** Thank you for being one of the compassionate who make this work possible.

Make your tax-deductible gift today by visiting **makeagift.ucsf.edu/magazine**

PHOTO: STEVE BABULJAK; ART: UCSF BENIOFF CHILDREN'S HOSPITAL PATIENT

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