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**INNOVATIONS IN RESEARCH, HEALTH CARE AND EDUCATION**

**VOLUME 9 / 2019**

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**The Next Fifty Years**

A LETTER FROM DAVID A. BRENNER

**THIS YEAR MARKS THE BEGINNING of the next half-century of growth and progress at UC San Diego School of Medicine.**

In 2018, we paused to note the 50th anniversary of SOM, highlighted over the course of the year by several significant events, such as the annual dean’s symposium, alumni weekend and Founder’s Day. It was a time to justifiably celebrate a long list of distinguished faculty, staff and students and their multitudinous achievements, all accomplished within a relatively brief period of time.

Now, it’s time to roll up our sleeves and resume doing what we do best: teach new generations of doctors, provide leading-edge, compassionate care to patients and develop the science and tools that make both things possible.

This year marks the beginning of the next half-century of growth and progress at UC San Diego School of Medicine. In 2018, we paused to note the 50th anniversary of SOM, highlighted over the course of the year by several significant events, such as the annual dean’s symposium, alumni weekend and Founder’s Day. It was a time to justifiably celebrate a long list of distinguished faculty, staff and students and their multitudinous achievements, all accomplished within a relatively brief period of time.

Now, it’s time to roll up our sleeves and resume doing what we do best: teach new generations of doctors, provide leading-edge, compassionate care to patients and develop the science and tools that make both things possible.

We do it under the guidance of Dr. Steve Garfin, who was named interim dean of the School of Medicine in early 2018. Steve joined the faculty in 1981. He is an internationally recognized leader in academic orthopedic surgery whose talents, insights and leadership served him well as chair of the Department of Orthopaedic Surgery (1997 to 2018) and will do so again as dean. With Steve leading the way, the next 50 years is off to a bright start.

Apropos of the new half-century, this issue of Discoveries has a fresh look and, in some ways, a refreshed mission. First published in 2010, the magazine’s primary purpose has always been to chronicle and disseminate the great thinking and doing of faculty, students and staff at UC San Diego Health, School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. Discoveries is seen and read not just by faculty and local physicians, but by academic health care leaders and influencers across the country, and by friends and supporters.

That purpose remains unchanged, but we’ve tweaked the magazine’s presentation to provide a better glimpse of what happens here in classrooms, clinics and labs, one that is both more expansive and more in depth.

Let’s start with the latter. Inside, you will find lengthier stories on three topics whose import demands every word and more: the problem of pain, the dual challenges of pursuing an MD and a PhD and the rising menace of antimicrobial resistance. These are divergent topics, but they share at least one commonality: In all three, physicians, pharmacists and scientists at UC San Diego are leaders in their fields.

In between, there are shorter but also illuminating features: words of wisdom from female faculty members on the experiences and challenges of being a woman of science; a timeline of how UC San Diego Health doctors (and others) collaborated to save a man’s life; a Q&A with Breakthrough Prize winner Don Cleveland; an annotated explanation of what a brain scan reveals; and a peak at some of the fabulous, legendary scientific images produced by Tom Deerinck at the National Center for Microscopy and Imaging Research on campus.

We’ve added a new feature too: a short Facts & Figures report providing readers with important data in a visually friendly presentation that captures the breadth and depth of the enterprise where we work at what we love.

Fifty-one years ago, UC San Diego School of Medicine was mostly bare ground, the site of a former U.S. Army base. From it has arisen an institution ranked as one of the finest schools of medicine in the country and world, one that produces doctors and scientists of comparable stature and acclaim. No one can predict what the next half-century will bring, but I am certain of this: We will shine, as we long have.

Sincerely,

DAVID A. BRENNER, MD

VICE CHANCELLOR

UC SAN DIEGO HEALTH SCIENCES
EVERY MORNING WHEN SHE WAKES UP, Cristine Reddell experiences what she describes as a sharp pain that feels like it’s crushing her spine. It makes even the routine aspects of life, like doing household chores, difficult and daunting. Some days the pain is so bad that Reddell can’t even get out of bed.

At 10 years old, Reddell was diagnosed with severe curvature of the spine that was present since birth. Her spine is curved 60 to 65 degrees and rotated, causing chronic pain that has plagued her ever since.

When she was very young, Reddell was treated primarily with anti-anxiety medications, such as Valium. She refused to take an opioid-based pain reliever until she was 22 years old but, once she did, her dosages climbed until she was taking as much as 600 milligrams (mg) of morphine and 32 mg of dilaudid per day.

“The simplest way I can put it is that when you are taking opioid doses that high, the medication controls your life,” Reddell said. “If the pharmacy was late with my medication, everything would revolve around when I was going to be able to pick it up.”

That’s when Reddell decided she needed a change. She had been on high-dose opioids for almost a decade, and yet her pain was not necessarily better.

Her experience is not unique. One in every four people in the United States has suffered from pain lasting longer than 24 hours, according to the National Institutes of Health. That means pain affects more Americans than diabetes, heart disease, and cancer combined. At the same time, enough opioid prescriptions were dispensed in some parts of the U.S. in 2016 for every person to have one, according to the Centers for Disease Control and Prevention (CDC). The prevalence of opioids has led to a rise in their abuse and addiction, an issue now considered a national health crisis. According to the National Institute on Drug Abuse, more than 115 people in the U.S. die every day after overdosing on opioids, including prescription pain relievers, heroin, and fentanyl.

Both of these epidemics — chronic pain and opioid abuse — challenge and threaten both impacted families and health care providers, but how do we address one without worsening the other?

The Problem of Pain

Two epidemics — chronic pain and opioid abuse — have created crises for patients, families, doctors, health systems and entire communities. How do we address one without worsening the other?

BY GABRIELLE JOHNSTON, MPH, AND HEATHER BUSCHMAN, PHD
Where it starts

The vast majority of patients in pain are cared for by their primary care physicians, and most of them are ill-prepared to treat the problem. “I can tell you that most primary care residency training programs don’t even address this,” said Lynette Cederquist, MD, a physician specializing in pain management at UC San Diego Health. “These days, that’s like sending out an internist without training them how to manage diabetes.”

As a result, pain management and palliative care are medical specialties that have picked up where primary care leaves off. Pain management experts typically treat patients with non-cancer pain, usually due to injuries or surgical complications.

“Seventy percent of chronic pain patients are treated only by primary care physicians, so it’s a true minority that make it to see a real pain specialist,” said Cederquist.

Professionals in palliative care—relatively new specialty—provide symptom management and supportive care for patients with any type of chronic, progressive illness, such as cancer or arthritis. According to Cederquist, palliative care grew out of the realization that there are lots of patients who could benefit from hospice care, or care typically reserved for the final six months of life, but who were not actually terminally ill.

“People were skeptical about the idea of end-of-life hospice care in the beginning, and now we embrace this model of care. We show terminally ill patients endless compassion, but for the patients who are sticking around longer, not so much. Our chronic pain patients endure an incredible amount of suffering for years and decades. Why would we not have the same compassion toward them?”

For many people like Reddell, the struggle for a normal life is compounded by difficulties in finding effective treatments and medications.

“They get treated sometimes like drug seekers when they go to the emergency room for pain or to the pharmacy to get their medicines,” Cederquist said. “Nobody would do that to a dying cancer patient.”

Sometimes you need opioids

Most health care providers believe there is a time and place for opioids. They have seen these medications transform patients’ lives, from the quality of daily living to a more comfortable end-of-life experience.

“Ideally, we would like to dispel myths and help people reach a middle ground when it comes to treating pain with opioids,” said Rabia Atayee, PharmD, professor at Skaggs School of Pharmacy and Pharmaceutical Sciences at UC San Diego. “Like any other mediation, opioids have their risks and concerns and, of course, shouldn’t always be used for everyone in pain. But these medications are beneficial and effective for certain people.”

Atayee specializes in pain management and works with patients at Moores Cancer Center and Jacobs Medical Center at UC San Diego Health. Her research focuses on evaluating how opioids are used in hospitals and developing strategies to better manage opioid-induced side effects. When she prescribes opioids for patients in pain, she closely monitors them to ensure the medication is truly improving their quality of life.

“We show terminally ill patients endless compassion. Our chronic pain patients endure an incredible amount of suffering for years... why would we not have the same compassion toward them?”

—LYNETTE CEDERQUIST, MD

Ruth Waterman, MD, interim chair of the Department of Anesthesiology, also recommends opioids for some patients. But she wants data to tell her what will work best for a particular patient before exposing them to potentially toxic side effects or wasting time on medications that will not work in their specific case. To do this, Waterman uses pharmacogenomics: the matching of drugs (pharmac) with a patient’s unique genetic variations (genomics).

“We give patients a lot of drugs when they’re under anesthesia in the operating room, yet we don’t always have a clear idea how one person might metabolize those drugs differently than another, and thus where we might need more or be able to use less,” Waterman said.

For example, Waterman’s team is testing patients for variants of the CYP2D6 gene. This gene encodes a liver enzyme that metabolizes drugs, including opioids. Most opioids, such as codeine or hydrocodone, are ingested in what’s called a pro-drug form, meaning they need to be broken down by the CYP2D6 enzyme before they become active. Some people produce versions of this enzyme that work better than others.

People whom Waterman would consider “normal metabolizers” respond well to ordinary doses of an opioid, whereas “poor metabolizers” might take a lot of the drug, but it never gets broken down into its active form. As a result, “we make more informed decisions.”

Waterman said. “It’s not an exact science yet, but it’s something that we’re using now to help us make more informed decisions.”

Sometimes you don’t

While some people genuinely require opioids and can take them responsibly, many do not and cannot. Today, most pain management specialists will tell you that a large portion of their patients have a hard time complying with their opioid therapy protocol.

“The problem with opioids is that patients develop a tolerance, a resistance, to the drug’s pain-relieving effects,” said Mark Wallace, MD, chair of the Division of Pain Medicine at UC San Diego Health. “So many patients, like Cristine Reddell, find they gradually need higher and higher doses to get the same relief. So we’ve learned over the last 10 to 20 years that you don’t reach for the opiates first.”

Cederquist believes the first step in pain management is addressing any underlying psychological factors.

“Probably a third of the time, patients with chronic pain also have concurrent mood disorders, such as anxiety or depression,” Cederquist said. “Those conditions have to be treated along with the pain because they kind of feed off each other. If we don’t have these treatments in place, I can throw all the pills I want at the patient and they are probably not going to do that well.”

Physician-patient communication is also a key to reducing the number of opioids prescribed, according to the CDC. Last year, the CDC released 32 recommendations advising health care providers on how to safely provide opioid access for those who need them, while preventing their misuse.

“You need to set expectations, establish treatment goals, follow up with the patient and most importantly, establish an exit strategy,” said Wallace, who served on the CDC’s advisory council for the recommendations. “All of these steps are essential to making sure that the patient has a successful experience using these high-risk drugs.”
Opioid alternatives

When opioids are not the right choice, patients need alternative options. Atayee said, “I think we need to do a better job of filling that toolkit with more than just opioids, more than just medications that we can offer to patients.” Some potential tools include:

**NEUROMODULATION.** Some approaches to pain management aren’t complete alternatives to opioids, but are considered “opioid-sparing.” In other words, they help patients consume fewer opioids. One such option is a spinal cord stimulator.

> “I always tell my patients that during withdrawal from opioids, their pain will increase — that’s a withdrawal symptom,” he said. “It’s not that their pain is going to increase and stay there forever, but it will get worse for a period of time. I also try to get them to understand that we can help them through withdrawal. We can do it slowly. I can give eligible patients other medications, like cannabis, to try to calm it down.”

Spinal cord stimulators are a type of neuromodulation. They work by preventing pain signals from reaching the brain. But they aren’t meant for just any kind of chronic pain, and not typically for general musculoskeletal low back pain, despite the fact that that’s where the device is implanted. These stimulators work best for people with pain after nervous system injury.

**CANNABIS.** Wallace and his pain management team are also increasingly turning to cannabis as a means to alleviate pain — sometimes instead of opioids, sometimes in addition.

Clinical trials suggest cannabis can help alleviate neuropathic pain — one of the most common reasons a primary care provider will refer a patient to a pain management expert. Medical cannabis contains two of the compounds produced by the cannabis plant — tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is a psychoactive compound responsible for cannabis “high” feeling. CBD is a non-psychoactive compound believed to provide therapeutic benefits for anxiety, though studies have yet to provide clear evidence that it works for that indication.

Wallace has been using cannabis as an effective tool to help patients who want to lower or completely remove opioids from their pain management regimen through the withdrawal process.

> “What I was seeing is that I had a lot of patients who were very compliant. They were working with me, they were weaning off of their opioid, hanging in there, having withdrawal symptoms, but were hurting,” said Wallace. “So then I would say let’s add cannabis. I noticed that they would feel better and the withdrawal symptoms would actually go down.”

Almost two years later, Reddell has successfully lowered her opioid dose from 600 mg of morphine and 32 mg of dilaudid per day to a baseline dose of just 6 mg of dilaudid. Besides dilaudid, Reddell also has a combination of cannabis, spinal epidurals, swimming and yoga to complete her pain toolkit. She feels stronger, more flexible and mentally clear.

> “One thing that I have learned is that it’s important to be flexible and look at all treatment options available,” she said. “Most importantly, you have to trust yourself and your body, and hopefully have a health care provider who is able to present you with all the necessary information to make the best decision for yourself and your condition.”

**A new day**

After deciding that high-dose opioids weren’t working, Reddell started filling her pain relief toolkit with more than just pills. Working with Wallace, she began to slowly wean herself off opioids. About halfway through detox, severe withdrawal symptoms appeared — diarrhea, nausea, cold and hot flashes — and her pain increased. Wallace introduced her to cannabis. Working through withdrawal was probably the hardest time in my life; it was completely awful,” Reddell said. “Cannabis was a true lifesaver for me because it eased my symptoms and allowed me to continue detoxing.”

For Wallace, it’s never an easy decision to introduce cannabis to a patient taking high doses of opioids. He has struggled with the possibility that he might be switching one known addictive drug for another. Sometimes he has waited until the patient was totally off opioids before turning to cannabis as a pain remedy.

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**YOGA.** In addition to, or instead of, cannabis, non-invasive therapies such as psychological therapies, education, exercise, healthy living and sometimes even chiropractic care and acupuncture can aid patients in pain.

Douglas Chang, MD, PhD, professor of orthopedic surgery and chief of Physical Medicine and Rehabilitation Services at UC San Diego Health, specializes in helping people in pain find what works best for them, if possible without resorting to medications or surgery.

> Chang is a fan of yoga for pain. Yoga studios are accessible, easy to find, relatively affordable and open on evenings and weekends. They can also provide social support. He said people are more likely to go to yoga with a friend in their own community than drive alone to a specialized clinic for physical therapy appointments.

Chang and colleagues have published evidence of yoga’s benefits. In a randomized clinical trial, for example, military veterans with chronic low back pain who participated in yoga for 12 weeks reported mild improvements in their pain intensity, as well as reduced opioid use, compared to a control group that delayed yoga treatment. They are now expanding their research on the effects of yoga on neck and back pain in military personnel.

> “We need to do a better job of filling that toolkit with more than just opioids, more than just medications that we can offer to patients.”

—RABIA ATAYEE, PHARMD

**The Agony and the Essence**

To successfully treat persistent pain, researchers must contend with — and conquer — a critical and chronic underlying factor: inflammation.

**IN ONE APPROACH,** UC San Diego scientists are specifically targeting toll-like receptor 4 (TLR4), a protein that sits on the surface of cells like an antenna, searching for molecules that signal infection or tissue damage. These molecular danger signs bind TLR4 and trigger inflammation, in turn initiating a cascade of cellular events that can lead to chronic pain.

Tony Yashk, PhD, professor of anesthesiology, and Yuri Miller, MD, PhD, professor of medicine, discovered that a naturally occurring protein called apolipoprotein A-I binding protein (AIBP) also binds TLR4, outcompeting products of tissue injury. The researchers found that treating mice with a single spinal injection of AIBP — and thus switching TLR4 “off” — prevented cellular events associated with pain processing. The treatment alleviated chemotherapy pain in mice for two months with no side effects.

Similarly, Krishnan Chakravarthy, MD, PhD, assistant clinical professor, pain management specialist at UC San Diego Health, affiliated faculty member at UC San Diego Jacobs School of Engineering and co-director of the UC San Diego Institute for Engineering in Medicine’s Center for Mobile Health Systems and Applications, has found a way to inhibit TLR4. He’s working on DT-001, a drug that made it to Phase III clinical trials, where it was being tested as a treatment for sepsis. The drug was safe, but testing was discontinued after it was determined to be not particularly effective for treating sepsis or systemic bacterial infections. Like AIBP, DT-001 binds TLR4, thwarting its activation and preventing inflammation and pain. Chakravarthy believes DT-001 will be useful for preventing persistent post-operative pain and reducing the need for opioids after surgery. He has launched a clinical stage biotechnology startup company, Douleur Therapeutics, to help test the drug in clinical trials.

> “Opioids and most other pain medications simply dampen a person’s perception of pain. But the source of the pain is still there,” Yashk said. “At the same time, opioids also impairs a feeling of pleasure, which leads to their misuse and addiction. What’s so special about inhibiting TLR4 is that this approach actually modifies the pain-processing systems themselves. So, if you think of neuropathic pain as a disease, then we see this as truly disease-modifying. We’re blocking the underlying mechanism that causes pain, not just masking the symptoms.”
We must have perseverance and above all confidence in ourselves. We must believe that we are gifted for something and that this thing must be attained.

—MARIE CURIE

“I grew up in the central valley in California. There weren’t too many role models around in those days, but it had always been my intention when I grew up to go into medicine because I actually did have a role model. My mother’s best friend was a local pediatrician who worked out of her house and treated children. She was very smart and had a very successful career while raising her family, and I thought that was a pretty interesting career. She was smarter than all the other medical practitioners in town — she was a very unusual, intelligent and interesting woman.

When I became a professor, I was appointed to be on committees and since it was a man’s world, typically I was the only woman on the committee. In those days, you soon realized that if you had an idea that was novel, you’d have a better chance of having the idea accepted if you communicated it to some other (male) member of the committee and then they proposed it as their own. It’s a funny thing but, of course, in those days, if women were assertive, they were seen as aggressive. The same characteristics in a man would be looked at differently and just be seen as assertive. It definitely was a man’s world. Women were few and far between.”

—Marilyn G. Farquhar, PhD

“...I have had a wonderful experience in academia because I have had an incredible mentor, who is male and has always been my biggest advocate. He has always treated me like an equal and values work based on merit, not gender. I believe there are definitely advantages of being a woman in the workplace. Women have strong multitasking and interpersonal skills and the ability to manage across different levels. Nowadays, science is becoming more of a team science, and women are better equipped at this approach.”

—Christina Chambers, PhD, MPH
Today, women in science are more than likely to become successful. I would also advise that women take advantage of opportunities presented to them early in their career. Once established, you can be more selective of saying yes to things that are more relevant to your interests and specialties.

If you surround yourself with a network of successful women in science, you are more than likely to become successful.

—Jamila Stockman, PhD, MPH

In 2017, women comprised 44 percent of academic scientists (faculty, staff and postdoctoral researchers) and 54 percent of graduate students at UC San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences.

As a woman, and as a Latina, it was really challenging to find mentors who were like me. Many times, especially when I took advanced science and math courses, I was often the only woman or Latina in the room. It was daunting to see how underrepresented women are in this field. It’s a little lonely, especially in urology, which is dominated by men. On the flip side, I can be part of a field in which I can act as a pioneer and role model for others.

“I believe my generation of women in medicine has really benefited from the women who came before us and paved the way.”

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—Anita Raj, PhD

“Women today are able to be more vocal in the field of science than previous generations, which poses an additional set of challenges. We are being questioned more; being challenged about the particular topic we are discussing. Some women have a fear of voices too much of an opinion because they may be judged as being too aggressive. Today, women have to balance voicing their opinions and concerns with the potential for gender bias.

There is a lot to be learned from junior investigators who are entering the field and senior investigators who have a wealth of experience. They already had to overcome obstacles to get where they are in the field of public health. Junior investigators bring innovation and new methods to address old problems. Senior investigators have overcome many obstacles in the field and can provide guidance on picking your battles, dealing with challenges and forging a successful path in academia. If you surround yourself with a network of successful women in science, you are more than likely to become successful. I would also advise that women take advantage of opportunities presented to them early in their career. Once established, you can be more selective of saying yes to things that are more relevant to your interests and specialties.”

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Assistant Professor of Urology

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The UC San Diego School of Medicine Class of 2018 was 51 percent women, reflecting a nationwide trend and demographic shift. While practicing physicians over the age of 65 remain predominantly male (82 percent), more than 60 percent of doctors under age 35 are female.

PHOTOS BY ERIK JEPSEN

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PHOTOS BY ERIK JEPSEN
But there is a rare breed of learner who has the desire — and drive, determination and stamina — to earn both degrees and connect the worlds of research and patient care.

Since 1974, students at UC San Diego School of Medicine have been able to simultaneously earn their MD and PhD in the Medical Scientist Training Program (MSTP). Students participate in an integrated and individualized program of graduate training in biomedical sciences and clinical medicine. Careers with dual degrees can be found in academia, industry and government.

“UC San Diego was one of the nation’s first institutions to receive a training grant from the National Institutes of Health (NIH) to support its MD-PhD program,” said Paul A. Insel, MD, Distinguished Professor of Pharmacology and Medicine and co-director of UC San Diego’s MSTP. “With NIH support, we have been able to graduate more than 200 outstanding physician-scientists who are changing medicine globally.”

There is a long and continuing demand for physician-scientists, but the downside to pursuing this rigorous eight-year career path is the potential debt accrued. The average graduating debt of medical students is $183,000, according to the Association of American Medical Colleges. Factor in interest, and repayment amounts can approach almost half a million dollars. Now add the time and effort of adding a doctorate and the desire for financial well-being sooner than later can be a disincentive to seeking dual-degree training.
The curriculum emphasizes combining scientific discovery with medical practice. I started as a straight MD student. However, after doing elective research with Dan Storchberg at UC San Diego and with John Kane at UCSF, I decided to pursue the path of a physician-scientist and transitioned into the MSTP. I was named to the National Academy of Sciences in 2017. I often describe medical school as the ultimate survey course on life. As medical students, we are exposed to an extraordinarily broad sampling of human biology and disease from conception to death, along with associated social contexts. We graduate knowing a little bit about everything and not a lot about anything. I think that those experiences provide a perspective that is difficult to achieve through either training mechanism alone, and for me, it has strongly influenced my choice of scientific problems to work on. Primarily, Glass has investigated the development and function of macrophages—a type of white blood cell that plays key roles in immunity and in inflammatory diseases. A major line of investigation is to understand how the normally beneficial actions of the macrophage are subverted in inflammatory diseases, such as atherosclerosis, diabetes and neurodegenerative disease. Glass and colleagues have uncovered basic mechanisms that regulate both protective and pathogenic functions of macrophages that reside in atherosclerotic plaques and in the brain. He recently discovered how small genetic differences in regions of the genome that do not code for proteins can nonetheless influence the extent to which genes are turned on or off in different individuals and thereby influence risk of disease. These findings have implications for improved prediction, diagnosis and treatment of a broad spectrum of human conditions.
“For me, being an MD and PhD are deeply intertwined, but I think of my personality and identity as being more of a scientist than a physician. Scientists and physicians, by virtue of the environments in which they work, the time and evidence constraints they have to deal with, have to sift through evidence and make decisions in different ways. At this point, I think I do a decent job of toggling back and forth. I think a little bit like a physician in the lab, and a little bit like a scientist in the clinic.”

During her training, Nelson was skeptical that she would end up doing research that was related to her own patients, or vice versa, but in the end, almost without trying, it worked out that way. She has grown to appreciate this dual training and dual life.

“First, it turns out that the little things that patients mention during visits are really important. Patients and families can help you prioritize what aspects of disease are most important to figure out and treat, and they can also make observations about their own disease that give you clues about the underlying mechanisms. I love that I can come back to the lab and share these insights with my students. It helps us to hone in on important questions, and also helps keep us motivated in our work.”

“I also find that the combination of working in the lab, which often has a distant and unpredictable payoff, and working with patients and families, which can have more immediate gratification, keeps me excited and driven. Even when caring for patients and families with incredibly challenging diseases, I feel inspired by patients’ strength, and feel I can have an impact as an educator and supporter.”

These genes needed to be aggregated in some way to make sense of them biologically. Hsiao developed a hybrid engineering-statistical approach and wrote software to handle this kind of analysis and make it interpretable by biologists.

“Later, when I was a radiology resident at Stanford, I encountered a magnetic resonance imaging technique called 4D Flow, where we could capture a large amount of data about the movement of tissues and blood using MRI. Again, the problem was that we didn’t have a good way of interrogating the data to figure out what it meant for patients. Existing software was not designed for medical purposes, and took six to eight hours to analyze a single data set. So, I designed a completely new way of analyzing that data.”

Hsiao’s efforts led to a startup company called Arterys, which has partnered with GE Healthcare to bring the software to market. It is now an essential part of Hiasso’s daily clinical practice, and at several other hospitals nationally and internationally. Almost all patients who receive an MRI at UC San Diego Health with congenital heart disease have 4D Flow MRI as part of their evaluation and management.

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ON A SUNNY AFTERNOON last year, 25-year-old John Lozick, an avid cyclist, was riding his bike toward Pacific Beach. And then he wasn’t, crashing to the pavement, the victim of what would turn out to be a massive heart attack.

But Lozick was lucky. In those first and following moments, a diverse team of doctors, lifeguards, nurses, paramedics and others would come together, unapologetically and planned, to pull him back from the abyss.

**5 hours & 57 minutes**

**IN THE LIFE AND NEAR DEATH OF JOHN LOZICK**

**CHRONICLED BY MICHELLE BRUBAKER AND GABRIELLE JOHNSTON, MPH**

**5:20 PM**

**UNRESPONSIVE**

An unidentified doctor visiting from Las Vegas is driving behind Lozick when he sees the cyclist crash on West Mission Bay Drive. The doctor immediately pulls over, calls 9-1-1 and begins providing medical assistance. Lozick is unresponsive.

**5:24 PM**

**NO PULSE**

Kelly D’Lorenzo, MD, an emergency medicine resident at UC San Diego Health, is jogging and happens upon the scene. She stops to assist; determines Lozick has no pulse.

**5:29 PM**

**ASSESSMENT**

San Diego Fire-Rescue Engine 20 and AMR Medic 21 arrive; paramedics assess Lozick.

**5:30 PM**

**TRANSPORT**

AMR Medic 21 begins transport of Lozick to UC San Diego Medical Center in Hillcrest. Lozick remains unresponsive with no detectable heartbeat.

**5:44 PM**

**ADRENALINE INJECTED**

Paramedics inject epinephrine, a stimulant, into Lozick’s chest to restart the heart.

**6:05 PM**

**PULSE RETURNS**

Glober and team continue CPR and order tests, including markers for a cardiac enzyme that can help indicate arrhythmia, pulmonary embolism or myocardial infarction. Lozick’s pulse returns.

**6:15 PM**

**ECHOCARDIOGRAM & ELECTROCARDIOGRAM**

An echocardiogram and an electrocardiogram are performed. Glober observes the heart ventricles and the heart’s rhythm and has Lozick admitted to UC San Diego Medical Center in Hillcrest.

**6:21 PM**

**FAMILY HISTORY**

DiLorenzo had placed Lozick’s family in the ambulance. Inside, there was contact information. Doctors call Lozick’s sister, who says their father died from a myocardial infarction at age 32. This indicates a family history and the likelihood that Lozick may have undiagnosed heart disease.

**6:30 PM**

**CT SCAN**

To confirm a suspected diagnosis that Lozick had experienced a myocardial infarction similar to his father, a CT scan is ordered, but the results are inconclusive.

**6:40 PM**

**ARTERY BLOCKED**

An emergency coronary angiogram is performed in the cath lab. Laurence Ang, MD, an interventionist cardiologist, looks to identify any possible artery blockages. Lozick’s left anterior descending artery (LAD) is completely blocked.

**7:00 PM**

**STENT INSERTED**

Lozick is admitted into the hospital. A stent is inserted into the LAD to clear the blockage and restore blood flow.

**7:10 PM**

**DISCHARGED**

Discharged less than a week later, Lozick is feeling stronger every day, eating healthier and looking forward to getting back on his bike. “I cannot thank the individuals involved enough. It’s hard to put into words. It’s too emotional. It’s been a wild ride.”
FOR MORE THAN 40 YEARS, Tom Deerinck sweated the smallest of details: the placement of a cell beneath his microscope, the arrangement of organelles within that cell, the appearance of individual proteins within those organelles.

As a research scientist at the National Center for Microscopy and Imaging Research (NCMIR), based at UC San Diego, Deerinck provided collaborators with new perspectives and insights into life normally unseen.

He also earned countless national and international awards, including most recently the Lennart Nilsson Award, named after the late pioneering Swedish photographer who captured the previously uncaptured, including human development from the moment a sperm cell fertilizes an egg to birth. The Nilsson award is given by the Karolinska Institute, which also hands out Nobel Prizes.

Last year, Deerinck retired. These are some of his favorite images, described in his own words, and the imaging technology used.

The Universe of the Mind
The mammalian brain is one of the most complex objects in the known universe, with more than 100 trillion synaptic connections. Here is part of the hippocampus from a rodent brain, fluorescently labeled and digitally mapped to reveal its enormous complexity. Multiphoton fluorescence microscopy.
2. A Hairy Death
Apoptosis, or programmed cell death, is an essential part of life. It can be therapeutic too, as in the case of this dying cancer cell. The hairlike extensions are filopodia, used for sensing, migration and cell-cell interactions. Scanning electron microscopy.

3. The Immortal Cells of Henrietta Lacks
Almost 60 years after her death from cervical cancer, cells taken from Henrietta Lacks continue to be grown, sustained and studied in labs around the world. Dubbed “HeLa” cells, they are a mainstay of biomedical research in everything from infections to cancer to cloning. Confocal fluorescence microscopy.

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4. Synthetic Life
Although this simple, single-celled organism is only a small fraction of the diameter of a human hair, it represents a monumental milestone in biotechnology and synthetic biology. This bacterial cell possesses the smallest genome known. More profoundly, it represents the first synthetic species of life created by man. Based on the DNA blueprint of a naturally occurring bacteria, but highly streamlined, JCVI-Syn 3.0’s bacterial DNA was created with a computer and four common, off-the-lab-shelf chemicals by researchers at the J. Craig Venter Institute. Scanning electron microscopy.

5. Scourge of Humanity
The war against HIV has raged for more than three decades. A cure may finally be in sight. Here, a cultured human cell with HIV particles (purple) lurking on the surface. Scanning electron microscopy.

6. Stem Cell to Neuron
Pioneering work at UC San Diego is steadily advancing our knowledge and ability to harness the power of human pluripotent stem cells, seen here after transformation into a neuron in culture. Scanning electron microscopy.

7. Life Flight
Age-related decline of function is an inevitable hallmark of life. Or is it? Groundbreaking research by Michael Karin, PhD, Distinguished Professor of Pharmacology and Pathology, involving key genes in fruit flies may eventually lead to treatments that could vastly increase human longevity and quality of life. Scanning electron microscopy.

FACING PAGE:

8. Mouse Retina
Fluorescent markers highlight various cell components and the complex beauty of the optic fiber layer of a mouse retina. Quadruple confocal fluorescence microscopy.
The annual Breakthrough Prize ceremony is a red-carpet event intended to celebrate scientists who inspire and improve lives. The prizes in fundamental physics, life sciences and mathematics come with a whopping $3 million cash award, provided by the founders of Facebook, Google and 23andMe.

In 2018, one of the Breakthrough Prizes in life sciences went to Don Cleveland, PhD, Distinguished Professor of Cellular and Molecular Medicine, Neurosciences and Medicine and chair of the Department of Cellular and Molecular Medicine at UC San Diego School of Medicine. Cleveland has made seminal contributions to the understanding of how brain cells grow during normal mammalian development and how later defects in those mechanisms lead to neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS or Lou Gehrig’s disease) and Huntington’s disease.

Based on those findings, Cleveland and colleagues developed a new pharmaceutical partner, Biogen, and their larger pharmaceutical partner, Biogen, is conducting clinical trials in which they are suppressing tau as a means to treat Alzheimer’s disease. We want to get this work into human clinical trials. There couldn’t be a more exciting time. This is simply that perseverance pays off.

We will now develop this approach to multiple times in my career. And I think for me, and probably most scientists, those are the moments that are the most memorable.

What advice do you have for young scientists? You have to have two things to be successful: you have to have passion for doing it, and you absolutely, positively have to have perseverance. There are so many bumps. You just have to keep trying. Every piece of the work that led to our Breakthrough Prize was initially rejected by the big scientific journals. We just kept taking it further and further, with new models, additional diseases and new therapeutic approaches. And the lesson is simply that perseverance pays off.

What's next for your lab? Three things. First, we’ve just identified a gene that encodes a protein essential for regeneration of motor neurons after initial injury. We’ve shown it to be suppressed in almost 100 percent of ALS patients. We have determined how its synthesis is suppressed and how to re-activate it using our designer DNA drugs. These discoveries have identified what I think is the best gene disease target now for ALS. We want to get this strategy into human clinical trial.

Second, we want to determine the mechanism through which our designer DNA drugs get into cells. The textbooks say it shouldn’t happen, and yet it does happen throughout the cells of the nervous system. Then, if we figure out, perhaps we’ll find ways to enhance drug uptake so we could make this approach even more effective.

Third, with my colleague Xiang-Dong Fu, PhD, professor of cellular and molecular medicine here at UC San Diego School of Medicine, we’ve discovered how to use our designer DNA drugs to produce new neurons in the nervous system by converting one class of supporting cells — glial cells — into neurons. What we know today is just the tip of the iceberg of what will be achievable with this approach. But it opens the door for generating replacement neurons for those lost to age-related diseases of the nervous system. We will now develop this approach for human therapy. There couldn’t be a more exciting time.
Magnetic resonance imaging (MRI) uses powerful magnets and radio waves to create both wafer-thin pictures and three-dimensional models of the human body. Since its commercial debut in 1980, MRI has revolutionized medical imaging, nowhere more so than in the detection and diagnosis of neurodegenerative conditions, such as Alzheimer’s disease (AD) and frontotemporal dementia (FTD).

James Brewer, MD, PhD, is chair of the Department of Neurosciences at UC San Diego School of Medicine and director of the Shiley-Marcos Alzheimer’s Disease Research Center. He scrutinizes thousands of MRIs each year to diagnose whether a patient is suffering from clinical dementia or may be on the cusp. We asked him to look at a typical MRI scan — in this case, a single digital slice of the brain of a normal, 64-year-old man — and explain what he sees.

MRIs are initially analyzed by trained radiologists, who follow strict protocols to avoid overlooking any brain abnormalities or points of interest. “Such routine compensates for the human tendency to focus on expected issues and not look for what you’re not looking for,” said Brewer. Neurologists like Brewer then follow, comparing scans to other clinical data, such as clinical testing and patient interviews, to determine whether their suspected diagnosis is supported by MRI data.

THE DARK BLUE STRUCTURES ARE HIPPOCAMPI, a pair of seahorse-shaped structures that play important roles in memory. They are among the first brain regions to suffer damage from AD.

THE HIPPOCAMPI SIT AT THE BOTTOM OF TWO CURVING LATERAL CAVITIES OR VENTRICLES, one in each hemisphere, filled with cerebrospinal fluid (CSF), which circulates throughout the brain, removing metabolic waste and around it, cushioning the mushy brain from hard jolts against the skull. The average central nervous system contains just under six ounces of CSF — half in the brain, half in the spinal column. Brewer looks for signs of obstruction, perhaps caused by infection or internal bleeding, that can cause brain damage.

THE LARGER LIGHT GREEN AREA BELOW IS THE VENTRAL DIENCEPHALON, part of the forebrain. It manages fundamental functions like hunger and thirst.

THE CENTRAL BLUE-GRAY ORB IS THE PONS, part of the brainstem. It has major sensory roles in hearing, equilibrium and many facial movements, including expressions, swallowing, touch and pain.

THE DARK GREEN REGIONS BELOW THE CAUDATE NUCLEUS ARE THE THALAMUS, an important relay station for sensory information passing to the cerebral cortex – the primary regulator of consciousness, sleep and alertness.

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THE PINKISH-RED OUTER LAYER IS THE CEREBRAL CORTEX, the layer of tissue associated with memory, attention, perception, cognition, language and consciousness. Brewer looks for areas of thinning, which may indicate neurodegeneration. Different patterns indicate different diseases: thinning near the hippocampus suggests AD; thinning atop the frontal lobe may mean FTD.

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Mental Pictured

ZOOM: 955% ANGLE: 0     IM: 121/ 256 (A -> P)     THICKNESS: 1.00 MM     LOCATION: -7.50 MM

THE BLUE SPOTS ADJACENT TO THE LATERAL VENTRICLES ARE THE CAUDATE NUCLEUS, one for each hemisphere. They are associated with motor processes and some kinds of learning. They are a target of Huntington’s disease.

THE PAIR OF PURPLE STRUCTURES ARE THE GLOBUS PALLIDUS, involved in the regulation of voluntary movement. They are adjacent and connected to the pink putamen – both parts of the basal ganglia that initiates, controls and stops body movements.

BASIC MRIS APPEAR IN GRAY SCALE. A software program automatically adds color. Brewer doesn’t need the color to assess, but it shows that the computer is correctly differentiating brain structures and can assist when making some measurements.

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OUR BRAINS ARE WELL-CHARACTERIZED BY THEIR FOLDS AND CREASES, called gyri and sulci. Sulci are the grooves resembling fjords encircling the brain, filled with CSF. Brewer looks for signs they are widening abnormally. The brain naturally shrinks with age, but overly widening gyri and enlarging sulci might indicate neurodegeneration.

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Microbial resistance to the marvels of modern medicine is relentless and insistent, driven by the ancient imperatives of evolution. Bacteria live to change if change means survival — and bacteria have survived for a very, very long time. Indeed, for two billion years, they were the only life on Earth.

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Such adaptation happens everywhere, all of the time. A few years ago, researchers identified antibiotic-resistant genes in a sample of ancient Arctic permafrost. The genes conferred bacterial resistance to amikacin, an antibiotic invented in the 1970s. The microbe had encoded that resistance for a threat 6,000 years earlier — and kept it just in case.

The specter of antimicrobial resistance is well-known, not just to antibiotics no longer effective, but also to so-called “drugs of last resort.” In 2017, the Centers for Disease Control and Prevention reported more than 221 cases of virtually untreatable “nightmare bacteria,” capable of spreading genes that would make them impervious to all known antibiotics.

Such superbugs kill more often than not. More than 23,000 Americans die each year from infections caused by germs resistant to antibiotics; 1.5 million deaths occur worldwide. With large, the prospects appear terrifying. On average, a new infectious disease has emerged every year for the past 30 years. Unchecked, the World Health Organization estimates a post-antibiotic world might mean 10 million deaths annually by 2050, harkening back to the time of cholera and other plagues.

“All indicators suggest big trouble is coming,” said Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine at UC San Diego School of Medicine. “People have forgotten what life was like before penicillin. You could have a toothache and be dead in two weeks.” It’s a dark future for a past once so bright. When antibiotics debuted with penicillin in 1928, they were quickly dubbed wonder drugs. “Antibiotics are the most successful drugs of all time. They’ve cured more people than all other drugs combined,” said Victor Nizet, MD, professor of pediatrics and pharmacy at UC San Diego School of Medicine. But their overwhelming success, spurred by relatively rapid, easy drug discovery and development in the early days, has resulted in rampant overuse in both people and agricultural products. Seventy percent of all medically important antibiotics sold in the U.S. are given to animals, allowing bacteria endless opportunities to adapt, resist and survive.

Antibiotics have a singular purpose: Kill bacteria, good or bad. The analogy Nizet uses is chemotherapy. The first anti-cancer drugs targeted rapidly dividing cells — a hallmark of cancer biology — but they also killed blood, bone and hair cells, which divide frequently too. Early chemotherapy was a biological version of scorched earth. Antibiotics were presumed to be less toxic than chemotherapy, but the emergence of microbiome science has shown otherwise. Ill-advised use of antibiotics can effectively wipe out a healthy microbiome — the communities of beneficial and necessary microbial life that live on and within each of us — and what remains “is different and damaged,” said Varki.
Antibiotic use was, in a way, teaching and new pathogenic invaders. Ailments like allergies and asthma came, Nizet said. “On the other hand, the success of antibiotics had never stopped killing. “There were too many deaths for complacency in the antimicrobial resistance, so funding is limited and inconsistent. The pharmaceutical industry can do it, but it doesn’t look at antibiotic resistance as an economic target because, generally speaking, antibiotics aren’t profitable.”

Nizet agreed. “It’s a rather romantic notion that you’re going to discover an entirely new antibiotic drug. You have to be incredibly lucky, acquire millions of dollars in funding, show the new drug has no toxicity and even then, it takes years of clinical trials. Statistically, I will never happen across a new drug. The vast majority of researchers won’t. That’s why I think we need to rethink the entire definition of ‘antibiotic’ and reexamine our approach.”

A few years ago, a research team led by Bradley Moore, PhD, at SIO and Skaggs School of Pharmacy and Pharmaceutical Sciences at UC San Diego developed a “plug and play” method to genetically trigger previously unknown biological processes to help better identify potential drugs from environmental bacteria.

In 2016, scientists at the San Diego Supercomputer Center, based at UC San Diego, identified a potential new class of antibiotics that attacked bacteria in two ways: externally by destabilizing cells’ outer membrane and internally by crippling their ability to generate energy. At the same time, another team developed a method to determine if bacteria are susceptible to antibiotics within a few hours, an advance that could slow the appearance of drug resistance and allow doctors to more rapidly identify appropriate treatment.

Last year, researchers at the Center for Microbiome Innovation identified the mechanism used by clinically relevant bacteria to achieve antibiotic resistance — and created a model for predicting under which conditions it could spread. “The odds of finding new antimicrobials improve when using drugs already tested and approved,” Laws Eckmann, MD, professor of medicine, Sharon Reed, MD, professor of medicine and pathology, and colleagues have described creating more than 650 new compounds by slightly altering structural elements of metronidazole, a half-century-old class of antibiotic drugs used to combat everything from ulcer-causing stomach bacteria to gut-churning protozoa.

Many medications produce multiple therapeutic benefits. Statins, for example, were developed to lower blood cholesterol levels, but also fight some kinds of infection. Nizet, who reported the statins findings with Christopher Glass, MD, PhD, professor of medicine and cellular and molecular medicine, and colleagues said most serious infections involve a failure within the natural immune response, allowing the pathogen to get the upper hand. Drugs that boost general health may fix minor immune problems as well.

“If a drug has a big effect on a cell, it’s going to have a big effect on an invasive bacteria,” Nizet said.

In this manner, UC San Diego researchers have shown immune-boosting properties of the commonly prescribed breast cancer drug tamoxifen and blood thinner ticagrelor against antibiotic-resistant superbugs.

Nizet and collaborators have also been investigating the antimicrobial properties of anacardic acid, a compound in cashew nut shell oil long used in Asian folk remedies that appears to not just attack at least some types of infectious pathogens, but also boosts the host’s immune system.

Advances like high-throughput sequencing, systems biology and other bioinformatic technologies promise to further bump up the odds, but Pavel Pevzner, PhD, professor of computer science and engineering in the Jacobs School of Engineering, said every step forward further reveals the inherent challenges of chasing an elusive, shape-shifting adversary. In a 2018 paper published in Nature Microbiology, Pevzner and colleagues reported that two related bacteria are unlikely to produce identical peptidic natural products — the basis for many antibiotics and other bioactive compounds.

If peptidic natural product variants are much more diverse and numerous than suspected, the effort to develop drugs based upon them becomes correspondingly more complicated. It would be a case of more needles in the haystack, but also a lot more hay.
Antimicrobial peptides

Your skin is the first and most obvious barrier against infection, but what lies beneath may be more important. In 2015, a research team led by Richard Gallo, MD, PhD, Distinguished Professor and founding chair of the Department of Dermatology in the School of Medicine, discovered that dermal fat cells called adipocytes produce antimicrobial peptides (AMPs) that help fend off invasive bacteria and other pathogens.

AMPs are small packets of amino acid residues. More than 1,200 types have been isolated from animals, insects, plants and bacteria—all possessing antimicrobial capabilities. Their potency, in fact, has prompted Gallo to better describe them as “host defense peptides,” “alarmins” and “defensins.” AMPs not only kill microbes, they also control host physiological functions, such as inflammation and wound healing. Their multi-functionality—killer and healer—makes AMPs attractive as a new antimicrobial resistance weapon. Some approaches have been fairly simple. Infectious diseases like influenza and tuberculosis appear to be moderated by increased AMP expression, which in turn can be stimulated by higher levels of vitamin D.

Recently, Gallo and colleagues turned to friendly bacteria for another potential remedy. Staphylococcus epidermidis and Staphylococcus hominis are strains of skin bacteria that reside in ubiquitous harmony on most people’s skin. Both produce AMPs to help fend off other species, such as Staphylococcus aureus, a pathogen that aggravates a host of conditions and is, in its antibiotic-resistant form, the leading cause of death from infection in the United States.

In animal models and early phase clinical trials, UC San Diego researchers cultured S. epidermidis and S. hominis extractions from healthy skin and created a skin cream that was applied to patients with atopic dermatitis, the most common form of eczema. In all cases in the small phase I trial, the result was a significant decrease in S. aureus on participants’ skin. Phase II trials are underway to determine whether prolonged, repeated application of what Gallo calls “good” bacteria provides long-term benefit.

“Using a natural antibiotic produced by the skin microbiome is superior to current pharmaceutical approaches because the bacteriotheraphy does not kill protective bacteria strains,” said Teruaki Nakataki, PhD, a project scientist in Gallo’s lab.

“Antibiotic resistance is not likely to occur because the bacteria are attacking pathogens by multiple ways at once.”

Bacteriophages

In 2017, doctors and researchers at UC San Diego made international headlines by saving the life of one of their own with an antimicrobial therapy that was both new and old.

Tom Patterson, PhD, a professor in the Department of Psychiatry, had returned from vacation in the Middle East infected by a multidrug-resistant strain of Acinetobacter baumannii. Every antibiotic treatment failed. Patterson slipped into a coma. He was dying.

Spurred by his wife, Steffanie Straathof, PhD, an infectious disease epidemiologist and director of the UC San Diego Global Health Institute, Gallo’s research group turned to bacteriophages, a name derived from Greek for “eater of bacteria.”

“Phages” are viruses that selectively target bacteria. Each phage hunts a single bacterial species. There are more phages on the planet than all other organisms, including bacteria, combined.

In the early 20th century, European scientists already explored phage therapeutic potential, but the effort evaporated with the emergence of antibiotics. Phage therapy was consigned to the fringes of modern scientific inquiry.

With emergency approval from the Food and Drug Administration (FDA) and assistance from collaborators around the country, doctors astoundingly infused Patterson with a changing cocktail of purified phages derived from multiple sources, including sewage. Nothing like it had ever been done in the U.S. Within days, with no apparent ill effects, Patterson revived and ultimately recovered.

“A handful of similar cases followed: all patients suffering from multidrug-resistant or chronic bacterial infections. Every case was an experiment. Results varied, but were broadly encouraging. Late last year, with funding support from the UC San Diego chancellor’s office, Strathof, Schooley and colleagues launched the Center for Innovative Phage Applications and Therapeutics or IPATH, the first such enterprise in North America.

IPATH’s goal is to leverage their hard-won expertise into a systematic process that produces a new way to fight bacterial pathogens. “Clinical research will be integrated with translational and basic research to provide critical insights into the mechanisms by which phages selectively kill their bacterial targets,” said Schooley.

“That will accelerate the development of more advanced clinical research that we hope will lead the FDA to make phage therapeutics more widely available.”

“Of course, this requires a lot of things: clinical trial infrastructure and design expertise, microbiome expertise, a patient population needing novel interventions who wish to join us in this journey.

Although all of these elements are here, we plan to work with a wide range of partners around the world to advance these therapeutic from an anecdote to a globally available tool to combat the rising tide of multidrug-resistant infections.”
CHARM offensive

True to their view that conquering multidrug resistance will require multiple efforts, Nizet and colleagues hope to soon launch the Collaborative to Halt Antibiotic-Resistant Microbes, or CHARM, a campus-wide research and educational initiative to support a wide range of innovative scientific and outreach strategies.

“Our goal is to showcase UC San Diego, its partner institutions and the robust biotechnology community on the Mesa as a national leader in this crucial field of medical discovery,” said Nizet.

“We will make CHARM a streamlined library of expertise, a go-to place for quick, nimble analysis of a potential new target, of a drug’s abilities and functions.

We want to answer the question: Does this therapy have potential? Is it worth pursuing?”

CHARM investigators span the campus and include Joe Pogliano, PhD, professor of biological sciences, and Stephanie Frealy, PhD, assistant professor of bioengineering, who are inventing new methods to instantly identify superbugs and their resistance mechanisms through high-resolution microscope, microfluidic and machine-learning, thus speeding diagnosis and the appropriate therapy for patients.

More broadly, Elizabeth Winzler, PhD, professor of pharmacology and drug discovery in the Department of Pediatrics, and James McKerrow, MD, PhD, Distinguished Professor and dean of the Skaggs School of Pharmacy, are expanding the scope of the initiative to parasitic infections in the developing world, such as malaria and leishmaniasis.

In 2018, the university opened the new Center for Anti-Parasitic Drug Discovery and Development.

Given the global threat of antimicrobial resistance, the efforts of CHARM are not constrained by local geography or provincial perspectives. The initiative is establishing partnerships with top academic research centers in Europe, China, India, Australia and Latin America. UC San Diego scientists are also collaborating with entities like CARB-X, perhaps the largest public-private partnership in the world dedicated to preclinical antibiotic development, with seven partners in the U.S. and United Kingdom and more than half a billion dollars in funding.

“CARB-X helps small companies and academic laboratories with particularly innovative approaches gain a foothold to try out their concepts, understanding the high risk, but also the potential for true breakthroughs in antibiotic therapy,” said Nizet.

“UC San Diego is currently participating in a number of CARB-X-funded programs in partnership with local biotechnology companies.”

It will take every effort, current and yet-to-be imagined, to curb the threat of antimicrobial resistance.

Humans are outnumbered. Estimates of the global population of bacteria — 5,000,000,000,000,000,000,000,000,000,000,000 — are higher than for all of the stars. Millions of microbes remain to be discovered. Our understanding is limited to the tiny fraction that scientists have learned to culture in labs.

In 1962, during the heyday of antibiotics, an Australian immunologist and Nobel laureate declared “the virtual elimination of the infectious diseases as a significant factor in social life.”

But something changed. Bacteria. Then changed again. And so the fight goes on, ever-evolving and likely ever the same.

Pavel Pevzner, PhD, professor of computer science and engineering at Jacobs School of Engineering

Philanthropy: LOOKING BEYOND

In 2018, U.S. News & World Report ranked University of California San Diego the fifth best public university in the nation and 17th best in the world, taking particular note of high-performing academic areas in the health sciences, such as pharmacology and toxicology, neuroscience and behavior, microbiology, molecular biology and genetics, psychiatry and psychology, clinical medicine, immunology and public health.

In August, Viterbi donated $50 million to UC San Diego to name The Viterbi Family Department of Ophthalmology and The Viterbi Family Vision Research Center, and to create six endowed faculty chairs. The former is the first named Health Sciences department at UC San Diego, the latter will be a new facility focused on ophthalmological research, such as curing glaucoma blindness and restoring vision lost to retinal degeneration, cataracts and infection.

“I am honoring my father’s memory,” said Viterbi. “He struggled to make a home for us in a new world, and now I aim in the position to honor his name.”

Dr. Herbert and Nicole Wertheim Foundation

Wertheim founded the world’s largest manufacturer of ophthalmic instruments and diagnostic tools for eye care. He invented UV-blocking eyeglass tints. These successes have allowed him and his wife, through their foundation, to pursue a second life in philanthropy, donating more than $400 million to various causes since 1977.

In October, the Wertheim Family Foundation pledged $25 million contingent on establishing a new school of public health at UC San Diego. The proposed school would be the third on the Health Sciences campus, joining the School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences. The gift also supports current efforts to expand critical faculty, increase educational offerings and fund key research.

“The most important thing we can achieve is making our communities healthier across the lifespan, and thus more productive,” said Wertheim. “Prevention is, and always will be, the best medicine.”

Andrew J. Viterbi

Viterbi attended and has taught at several powerhouse U.S. universities, including UC San Diego, becoming along the way a communications pioneer who helped develop key algorithms and applications that power cell phones and other wireless technologies today.

But he recalls his past too, in particular his father: Dr. Achille Viterbi, who escaped fascist Italy with his family in 1919 to rebuild his career as an ophthalmologist in America. In October, Viterbi donated $50 million to UC San Diego to name The Viterbi Family Department of Ophthalmology and The Viterbi Family Vision Research Center, and to create six new endowed faculty chairs. The former is the first named Health Sciences department at UC San Diego, the latter will be a new facility focused on ophthalmological research, such as curing glaucoma blindness and restoring vision lost to retinal degeneration, cataracts and infection.

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School of Medicine gets new interim dean, department chairs
Steven Garfin, MD, was named interim dean of the UC San Diego School of Medicine, succeeding David A. Brenner, who remains as vice chancellor of health sciences. Garfin is an internationally recognized leader in academic orthopedic, who joined the School of Medicine in 1981 and served as chair of the Department of Orthopedic Surgery from 1997 to 2018. Dr. Reid Abrams was subsequently named to serve as interim chair of the department. James B. Brewer, MD, PhD, was named chair of the Department of Neurosciences, UC San Diego Health, and chief of the division of neurosurgery, Department of Surgery in the School of Medicine. Ruth S. Waterman, MD, MS, was named interim chair of the Department of Anesthesiology at UC San Diego School of Medicine and at UC San Diego Health. California’s first accredited geriatric emergency department
The Gary and Mary West Emergency Department (pictured above) at UC San Diego Health, UC Irvine Health and the California Precision Medicine Consortium. Lucila Ohno-Machado, MD, PhD, (pictured above) leads the All of Us Research Program at UC San Diego Health. In 2018, she was also elected as a national database to inform thousands of future studies covering a wide variety of human conditions. In California, the All of Us program is headed by UC San Diego Health, UC Irvine Health and the California Precision Medicine Consortium.

Pioneering trials for leukemia and spinal cord injuries
Stem cell scientists in the School of Medicine reported encouraging findings from a pair of first-in-human phase I clinical trials.

In one, researchers reported that treatment with cirmtuzumab, an experimental monoclonal antibody-based drug developed by Thomas Kipps, MD, PhD, (pictured above), Distinguished Professor of Medicine and deputy director of research at UC San Diego Moores Cancer Center, and colleagues measurably inhibited the “stemness” of chronic lymphocytic leukemia (CLL) cells — their ability to self-renew, resist treatment and recur. CLL is the most common form of blood cancer in adults. In the second, researchers reported that neural stem cells transplanted into participants with chronic spinal cord injuries produced measurable improvement in three of four subjects with no serious adverse effects. Both trials have progressed to new phases.

CBD for autism? TBD
In a first-of-its-kind investigation, researchers in the School of Medicine, with collaborators, will determine if and how cannabidiol (CBD), a non-psychoactive compound found in the cannabis plant, provides therapeutic benefit to children with severe symptoms of autism spectrum disorder. The findings have potential to provide new treatment options for countless children with neurodisabilities and may be foundational to the emerging field of cannabis therapy.

Epidemiologist named to TIME’s Health Care 50
Steffanía Strathdee, PhD, an infectious disease epidemiologist and director of the UC San Diego Global Health Institute, was named to TIME magazine’s inaugural 50 Most Influential People in Health Care for her work advancing the use of bacteriophages to treat multidrug-resistant infections. Read more on page 35.

Lewy Body Dementia expertise
UC San Diego Health has been named a Lewy Body Dementia Association Research Center of Excellence, joining a network of 24 preeminent academic medical research centers in the US focused on studying and treating one of the most common forms of dementia. The designation provides a centralized, coordinated research resource, clinical trials support and boosted expert care for patients, families and caregivers. LBD affects an estimated 1.4 million individuals in the U.S.

UC San Diego Health Sciences Academic and Clinical Enterprises

Facts & Figures
World Leaders in Scientific Output, Life Sciences 2018

MOST PROLIFIC COUNTRIES AND AMERICAN UNIVERSITIES

1. United States 8,472
2. UK 1,368
3. Germany 1,197
4. China 1,151
5. Switzerland 684
6. France 651
7. Canada 552
8. Australia 386
9. UC San Diego 172
10. UCSF 172

TOTAL CLINICAL TRIALS

Approx 2,400

PATIENTS IN ACTIVE TREATMENT

Approx 7,000

ACTIVELY ENROLLING TRIALS

Approx 1,000

NEW TRIALS ANNUALLY

Approx 250

Source: 2018 Nature Index

UC San Diego Research Awards by Campus Area — $1.2B in FY18

HEALTH SCIENCES

$686 MIL

68%

GENERAL CAMPUS

$280 MIL

20%

SCRIPPS INSTITUTION OF OCEANOGRAPHY

$155 MIL

14%

UC San Diego Health Academic Enterprise

CLINICAL TRIALS

2,400

7,000

1,000

250

World Leaders in Scientific Output, Life Sciences 2018

Source: 2018 Nature Index

UC San Diego Industry and Economic Impact

STARTUPS LAUNCHED IN ’17 WITH UNIVERSITY TECHNOLOGY

40

FORTY-TWO

ROYALTY INCOME

3,089

ACTIVE INVENTIONS

NEW PRODUCTS AND SERVICES

22

ANNUAL SALES OF LOCAL, UNIVERSITY-RELATED COMPANIES

$32.4B

LARGEST EMPLOYER BASED IN SAN DIEGO

2

CAMPUS IS SECOND AMONG ALL UCS IN NUMBER OF PATENTS ISSUED IN FY16

ONE

THE HEALTH SCIENCES DRIVE THE MAJORITY OF THE UNIVERSITY’S PARTNERSHIPS WITH INDUSTRY

UC San Diego Innovations and Technology Transfer

UC SAN DIEGO HEALTH

RESEARCH

ROYALTY INCOME

COMMERCIALIZATION

NEW  STARTUP COMPANIES UTILIZING LICENSED TECHNOLOGY, IN FY17

PROCESS YIELD:

ACTIVE INVENTIONS

3,089

NEW PRODUCTS AND SERVICES

22

ACTIVE U.S. PATENTS

897

THE HEALTH SCIENCES DRIVE THE MAJORITY OF THE UNIVERSITY’S PARTNERSHIPS WITH INDUSTRY

UC SAN DIEGO HEALTH SCIENCES

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UC SAN DIEGO HEALTH SCIENCES

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UC San Diego Health, Innovations in Care

NEW MEDICATIONS AND DIAGNOSTICS BASED ON UC SAN DIEGO RESEARCH

<table>
<thead>
<tr>
<th>TOP EARNING MEDICAL PATENTS</th>
<th>LICENSING PARTNER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elmiron, treatment for interstitial cystitis</td>
<td>Ortho-McNeil</td>
</tr>
<tr>
<td>Erbitux, cancer therapy based on EGF receptor antibodies</td>
<td>Ev Lilly</td>
</tr>
<tr>
<td>Procysbi, treatment for nephropathic cystinosis</td>
<td>Harman Pharma</td>
</tr>
<tr>
<td>Lymphoseek, lymphatic mapping for cancer care</td>
<td>Navidea Biopharmaceuticals</td>
</tr>
<tr>
<td>TearLab Osmolarity Test for dry eye disease diagnosis1</td>
<td>TearLab</td>
</tr>
</tbody>
</table>

Cumulative Royalties through 2017: > $175M

1 Led by UC San Diego Jacobs School of Engineering

SAN DIEGO STARTUPS BASED ON UC SAN DIEGO DISCOVERIES

<table>
<thead>
<tr>
<th>RESEARCH DISCOVERY</th>
<th>BIOMEDICAL STARTUP (year founded)</th>
<th>ACQUIRED BY (year founded)</th>
<th>AMOUNT</th>
</tr>
</thead>
</table>

Achievements, Charity Care and Other Benefits to the Community

<table>
<thead>
<tr>
<th>COMMUNITY BENEFIT</th>
<th>PROGRAM AND SERVICES PROVIDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student-run free clinic and medical translation services and community health events</td>
<td>$2,740,000</td>
</tr>
<tr>
<td>Subsidized health services</td>
<td>$2,174,000</td>
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<tr>
<td>Education of health professionals</td>
<td>$50,470,000</td>
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<tr>
<td>Government-sponsored care shortfalls</td>
<td>$155,208,000</td>
</tr>
<tr>
<td>Uncompensated care</td>
<td>$49,863,000</td>
</tr>
<tr>
<td>Charity care and other community benefits include:</td>
<td>$260.5M FY2017</td>
</tr>
</tbody>
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UC San Diego Health Sciences comprises the region’s only academic health system, one of the nation’s top research-intensive schools of medicine and the Skaggs School of Pharmacy and Pharmaceutical Sciences.

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