VOLUME 08 2018

DISCOVERIES

UC SAN DIEGO
SCHOOL OF MEDICINE
1968 – 2018

UC San Diego Health

DISCOVERIES

INNOVATIONS IN RESEARCH, HEALTH CARE AND EDUCATION
VOLUME 8 / 2018

This year, UC San Diego School of Medicine hits 50. Still young, as institutions go, but in that half century, the study and practice of medicine have changed dramatically.

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NINETEEN HUNDRED AND SIXTY-EIGHT was a tumultuous and memorable year.

North Korea captured the USS Pueblo and crew; North Vietnam launched the Tet Offensive. Martin Luther King, Jr. was assassinated. Upon hearing the news a few hours later, just as he was about to give a scheduled speech, Sen. Robert F. Kennedy responded with a powerful extemporaneous eulogy in which he called upon those who would "tame the savageness of man and make gentle the life of this world."

Far above, Apollo 8 became the first manned spacecraft to orbit the moon.

And below in 1968, University of California San Diego School of Medicine opened its doors with a charter class of 47 students. Built upon the churned ground of a former U.S. Army base called Camp Matthews, UC San Diego School of Medicine was only the third in the UC system. It remains today the only such institution in San Diego.

The issue of *Discoveries* you hold celebrates the 50th anniversary of what is affectionately known as SOM. There is much to celebrate. In just 50 years—a blink of the eye, really—this place and the thousands of faculty, staff and students who have labored and learned together have created SOMething remarkable.

I first came here in 1985 on a fellowship in gastroenterology. The school was unlike any previous or subsequent learning experience, which no doubt was the purposeful intent of its visionary founders, people like Kurt Benirschke, Helen Ranney and Eugene Braunwald. SOM was a home for bold people with bolder ideas, who wanted to reimagine and revivify the teaching of medicine, the training of doctors and the mission of conquering disease.

"We were and are unique," says John West, MD, PhD, DSc. John should know. He has been at SOM since practically opening day. He is a much-honored pioneer in physiology, specializing in the effects of high altitude (or space) on lung function. He still teaches.

"We've always tried to do things a bit differently," John says. "From day one, medical school students are taught by clinical scientists and working researchers. There's a deep, long-standing, inextricable connection here between the science and the art of medicine. The curriculum has always been about making it real—and about making really good doctors and scientists."

SOM ranks among the top 20 schools in the nation and in the world. Not bad for a place born the same year the 747 Jumbo Jet first took off. You can read about some of the work and achievements that helped launch our enterprise in this issue—and which continue to keep us flying high. The School of Medicine and, more broadly, UC San Diego Health, has been the catalyst for exciting, extraordinary research and advanced, compassionate medical care, from creating dramatic new surgical techniques, like pulmonary thromboendarterectomies and multi-organ transplants to illuminating the inner workings of cells in real time to realizing the enormous potential of stem cells and RNA to remedy what ails us.

On this page, you can see a short list of those who served before me as dean of the School of Medicine, some doing the groundwork prior to the actual opening of the school. Each in their way improved, elevated and grew the School. They would smile to see it now: bigger, better, bolder than ever. I won't presume to predict exactly where we will be 50 years from now, but will say this: Our future is as brilliant as our faculty and students. When I look ahead, I smile too.

Sincerely,

David A. Brenner, MD
Vice Chancellor, Health Sciences and
Dean, School of Medicine
University of California San Diego

An artistic rendering of the surface of a human dendritic cell, a key player in the body's adaptive immune response that is capable of deeply infiltrating tumors. As such, researchers are using dendritic cells in a variety of emerging immunotherapies.

Image courtesy of National Institutes of Health

The Cancer Journey

When Dennis Lyon's recurring back pain returned, he expected the usual diagnosis and treatment. He wasn't prepared for what magnetic resonance imaging revealed or what his medical team said next.

By Yadira Galindo

"Cancer is a genetic disease in which the DNA within cells mutate, enabling them to grow unchecked and spiral out of control."

–Kelly Frazer, PhD

Lesions were found on his lung and liver and later appeared in his brain. After a battery of tests, he was diagnosed with a rare form of metastatic basal cell carcinoma. He was told it was terminal.

Basal cell carcinoma is the most common type of skin cancer; it is usually highly treatable and does not spread beyond a small skin lesion. In fact, Lyon had been successfully treated several times for surface lesions, though his last bout with skin cancer had required three surgeries to remove deeper malignant cells.

"They finally stopped and said, 'We can't go any deeper or we'll damage your arm, so we're going to send you for radiation.' I was then told I was cured and that I shouldn't have any problems," said Lyon.

"Within about a year, I went back to my dermatologist and said, 'I feel something tingling where they did the surgeries. How do we know that you've killed the cancer if you never do a scan on my arm to see if there's anything going on?' I'll never forget, he said, 'Oh, you never have to worry about basal cell metastasizing. It just can't do that.'"

But it did. With the new diagnosis came a grim prognosis: Two years of life with treatment, one year without.

Lyon sought care at five different cancer centers hoping for a different outcome. At one center, he was treated with the only currently available therapy for metastatic basal cell carcinoma. It was ineffective. At other institutions, he enrolled in clinical trials, but his disease continued to progress. Lyon felt hopeless as doctor after doctor told him there was nothing more they could do.

As a last-ditch effort, he sought out Razelle Kurzrock, MD, director of the Center for Personalized Cancer Therapy and founder of the Rare Tumor Clinic at Moores Cancer Center at UC San Diego Health.

"I was told, 'This woman can perform miracles. She will throw everything at the wall to see what sticks. You need to see her,'" Lyon recalled.

Molecular Microscope

Using advancements in technology and genomic medicine, Kurzrock looks at the genetic makeup of tumors for mutations that can be targeted with existing drugs to stop cancer's unrelenting growth. It's an individualized approach: Every patient and every cancer is different. The genetic material in Lyon's tumor was revealing.

"What we found with Dennis was that his DNA was a mess," said Kurzrock. "Most patients have a few mutations. He had 100. That's why previous treatments failed."

Cancer is a genetic disease in which the DNA within cells mutate, enabling them to grow unchecked and spiral out of control, said Kelly Frazer, PhD, director of UC San Diego Institute for Genomic Medicine and founding chief of the Division of Genome Information Sciences in the Department of Pediatrics at UC San Diego School of Medicine. Cancer-causing mutations can be inherited. They can be due to errors that occur as cells divide. Or they can be the result of environmental factors, such as exposure to toxins or pollutants. The cellular consequences vary, making cancer treatment extraordinarily complicated. Genomic medicine, though, is creating new opportunities.

"In the last 15 years or so, the study of tens of thousands of tumor genomes has led to tremendous insight into understanding the underlying mechanisms that give rise to cancer," said Frazer. "Genomic medicine is an extension of the field of study of cancer genomics, relying on the same techniques but aimed at developing diagnostics that enable targeted treatment of specific cancers."

The field of cancer genomics has flourished as advancements in sequencing technology and high-performance computing allow for the generation of large datasets and their subsequent analysis, said Frazer. Tumor sequencing not only identifies mutated genes that may be driving tumor growth, but also provides insight into potential therapies, such as drugs designed to target specific cellular functions or dysfunctions.

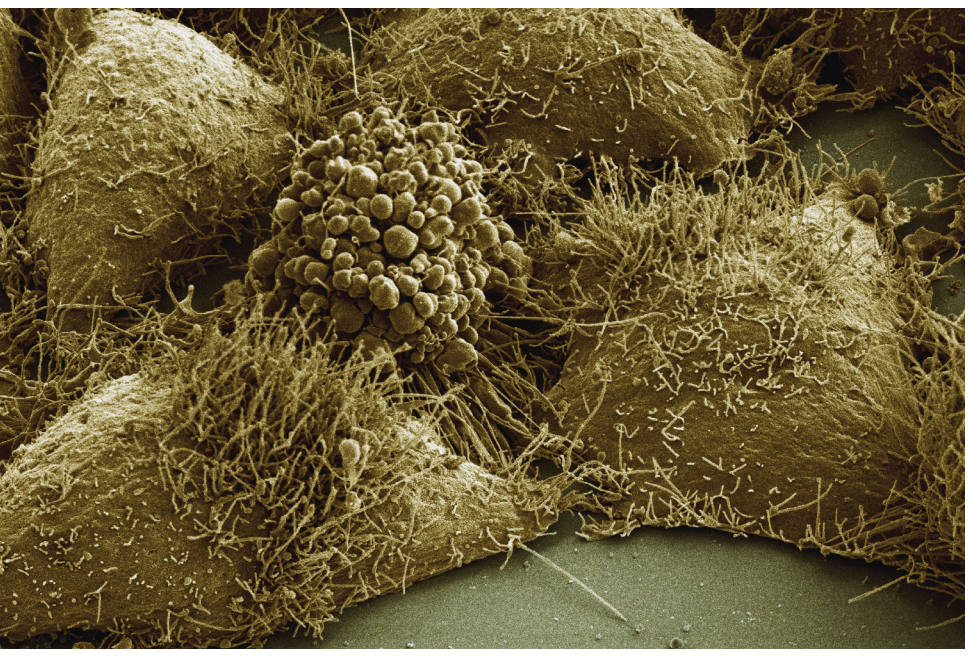
Kelly Frazer, PhD

Razelle Kurzrock, MD

For example, Thomas Kipps, MD, PhD, Evelyn and Edwin Tasch Chair in Cancer Research, discovered that chronic lymphocytic leukemia (CLL) exploits an oncogene dubbed ROR1—found on malignant B cells but not in normal adult tissues—to spread disease. When ROR1 is combined with another oncogene, it results in a faster-developing, more aggressive form of CLL. These findings led to the development of a monoclonal antibody that targets ROR1. The drug is in clinical trials now.

A study headed by Catriona Jamieson, MD, PhD, chief of the Division of Regenerative Medicine at UC San Diego School of Medicine and director of the Stem Cell Research Program at Moores Cancer Center, found an inhibitor that can stop the overproliferation of blood cells caused by mutations in the JAK2 gene that result in problems with blood clotting, heart attacks and, in some cases, leukemia. This drug has also undergone clinical trials, showing the ability of genomic technologies to identify new molecular targets that can lead to changes in diagnosis and new therapies.

"No other technology revolution has happened at this speed," said Kurzrock. "You need an accurate diagnosis, and genomics gives you that diagnosis. We now have tools we didn't have five years ago that allow us to see with precision what's wrong within each tumor and, as a result, we have more information to better determine which drugs to give to each patient. We also have a protocol that uses profile-related evidence to determine individualized cancer therapy so that precision treatment is accessible to many patients with lethal cancers and not just a select few."



A cultured HeLa cancer cell (center) undergoing apoptosis or programmed cell death. The globular objects are blebs, produced as the cell's cytoskeleton breaks up and causes the membrane to bulge outward.

Thomas Deerinck, NCMIR, UC San Diego

Data Translation

Supercomputers can analyze vast amounts of genomic data quickly and tirelessly, but interpreting that data requires people. A lot of them. The Molecular Tumor Board is a group of experts from diverse fields who scrutinize genomic information to determine the best therapy possible for an individual patient.

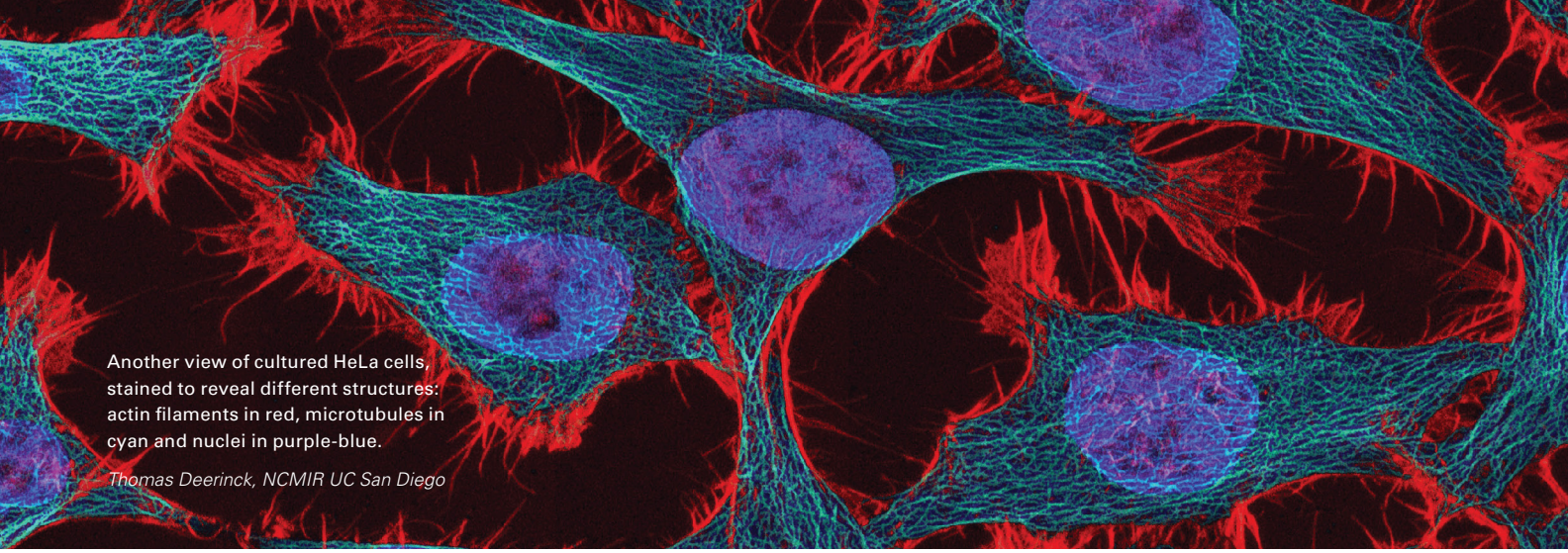
"If you go back five years, if we came across a case in which a patient had 100 mutations like Dennis, we would have hung our heads and said he was untreatable," said Kurzrock. "How do you target 100 mutations? I personally would have said that these tumors in which the DNA is completely chaotic would never be treatable. Who would have guessed that just a few short years later, these are the most treatable tumors?"

At the Board, oncologists are at the table with faculty from the San Diego Supercomputer Center at UC San Diego, along with geneticists, radiologists and other medical experts. They took on Lyon's case and, using genetic data from a blood and a tissue biopsy, his physicians were able to track pathological changes over time.

In cancer, fragments of tumor DNA are shed into the blood from the primary tumor, allowing researchers to evaluate multiple mutations from different metastatic lesions at once.

Based on his tumor's profile and the number of mutations, Lyon was prescribed an immune checkpoint inhibitor called nivolumab, which treats advanced cancers of the lung, kidney, blood, bladder, head and neck cancer, and melanoma. It is not currently standard treatment for basal cell carcinoma, but Lyon's tumor type had a genetic mutation that previous studies suggested might be responsive to nivolumab.

It was. Today, Lyon's tumors have shrunk by more than 90 percent, with very few side effects. He has a small spot on his liver and his brain. His physicians are unsure if these are remaining cancer tissue or scars. The other tumors have disappeared.



Another view of cultured HeLa cells, stained to reveal different structures: actin filaments in red, microtubules in cyan and nuclei in purple-blue.

Thomas Deerinck, NCMIR UC San Diego

"I truly believe that our generation is going to solve cancer… The next generation is going to view cancer as curable or at least as a completely manageable disease."

– Ezra Cohen, MD

Immunotherapy

Some cancer cells have the ability to circumvent the immune response, persist and even adapt to treatment. Scientific advancements are helping patients like Lyon fight back by boosting the abilities of the immune system to recognize and destroy cancer cells. It's called immunotherapy.

"The accumulation of mutations results in expression of mutant proteins that are presented on the surface of the cell and serve as targets for the immune system," said Ezra Cohen, MD, Moores Cancer Center associate director for translational science. "For decades, these targets were elusive, but we're now producing deep and sometimes complete responses in advanced malignancies that previously showed no results or were resistant to therapy."

At present, the number of immunotherapy patients who experience dramatic responses is few. But new research promises improved effectiveness, said Cohen. With a robust immunotherapy clinical trial program, investigators at Moores Cancer Center are studying different technologies in cooperation with the body's biological response to confront the multiple defenses of cancer.

Some patients need combinations of therapies, such as checkpoint inhibitors, with immune system boosters or perhaps a cancer vaccine. All of which are being investigated or under development at Moores Cancer Center.

Cohen is leading one effort to create personalized vaccines. His team is investigating neoantigens—foreign protein fragments—that can reveal cancer cells to the immune system. They want to produce vaccines based on these neoantigens to restimulate the immune system to respond and attack.

"We will let biology decide which neoantigens to attack," said Cohen. "This isn't a dream or fantasy. This is about to happen in real patients."

Cell therapy is another approach. Already activated T cells are harvested from patients, cultured and mass produced in the lab, then infused back into the patient, providing them with a reinforcing army of T cells. Another approach involves engineering naïve (inactivated) T cells with a chosen receptor that targets a surface marker on a cancer cell. Creating natural killer cells from stem cells is yet another option being investigated by Dan Kaufman, MD, PhD, director of cell therapy.

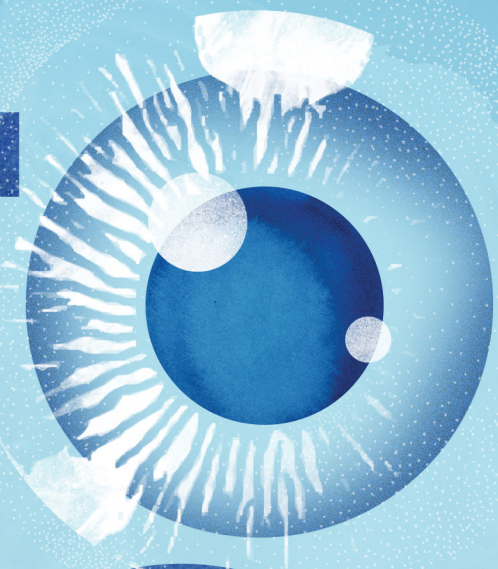
A Future

Fifty years ago, chemotherapy promised to be the answer to cancer, and sometimes it was. But the drugs used were often highly toxic and indiscriminate. With each decade, new therapies with less toxicity and longer, better response times have emerged. There is a greater and deeper understanding of the molecular drivers of cancer, which has led to targeted therapies and ideas like checkpoint inhibitors.

"Although it seems extreme right now, I truly believe that our generation is going to solve cancer," said Cohen. "The next generation is going to view cancer as curable or at least as a completely manageable disease."

Lyon certainly hopes so. "I might be in an era where I can get through this tunnel," he said. "If I had cancer 10 years ago, I wouldn't be here. UC San Diego is leading the way. My doctors will keep trying until they hit the target."

FOR SIGHT



At Shiley Eye Institute, vision means many perspectives and myriad possibilities.

By Jennifer Sturak

For poets and philosophers, eyes are windows to the soul. For ophthalmologists, the view is more pragmatic but perhaps more revealing. The eyes are windows into the body, revealing a host of health issues.

Robert N. Weinreb, MD

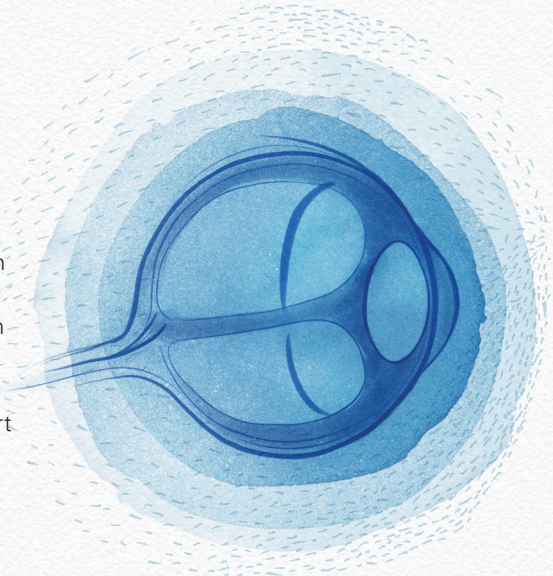
That view is clearer than ever, thanks to molecular genetics, advances in stem cell science and new imaging techniques. In combination, these technologies are allowing researchers at UC San Diego School of Medicine and the Shiley Eye Institute to not just see new ways to treat eye diseases, but to predict who is most likely to develop blindness and, eventually, to prevent it.

The institute's director, Robert N. Weinreb, MD, Distinguished Professor of Ophthalmology, has built a department focused on translational medicine, with faculty partnering with researchers across UC San Diego's La Jolla campus—engineers, computer scientists and neurologists—and beyond. When Human Longevity Inc. (HLI), the genetics-based health care firm located just a couple miles away, began looking to sequence the genomes of people with ready-to-go clinical histories and blood samples, Shiley scientists raised their hands and said, "Look to us."

BIG DATA BEFORE BIG DATA

For more than 25 years, Weinreb and colleagues have been observing patients through a longitudinal glaucoma study, known as the Diagnostic Innovations in Glaucoma Study (DIGS), and since 2012, they have been building the Shiley Eye Institute BioBank, led by director Radha Ayyagari, PhD, professor of ophthalmology and pathology and an expert in molecular genetics.

The BioBank has become a repository of thousands of small vials, stored in freezers, representing more than 5,000 patients with common eye conditions, including glaucoma and retinal diseases. Accompanying the blood samples are detailed clinical histories. Ayyagari calls it "deep phenotyping," gathering extremely detailed records about how a disease may manifest throughout the body.



"When you have large volumes of data on patients, you can learn about multiple aspects of these diseases, and use that information to make connections and provide care to other patients," said Ayyagari. That means a physician can adjust treatment or modify risk factors, such as smoking or sun exposure. A patient at risk of developing severe macular degeneration could perhaps delay the worst effects by several years."

The BioBank provided de-identified blood samples from approximately 1,600 BioBank participants to HLI, which has generated full-genome sequences, opening new research vistas.

> **"When you have large volumes of data on patients, you can…make connections and provide care to other patients."**
>
> — RADHA AYYAGARI, PhD

Just as cancer researchers identified the gene mutations known as BRCA—hereditary mutations associated with an aggressive form of breast cancer—eye researchers are looking for markers that indicate who is most likely to develop serious eye diseases and may need early, preventive treatment. Researchers have identified the genes whose mutations contribute to disease in perhaps half of patients with inherited retinal disease. For glaucoma, they are still searching for any kind of biomarker.

Just as every cancer is different in every patient, people do not lose vision exactly alike. Weinreb and colleagues say the goal is not simply to identify those who are predisposed to developing a blinding disease, but to also predict how they will respond to a particular medication and thus personalize their treatment. "But you need a large volume of data," said Ayyagari. "So we are trying to save samples suitable for analyzing all known markers today, but also for something that may become known tomorrow."

Eventually, the hope is to use new gene-editing techniques, such as CRISPR-Cas9, to prevent disease entirely. Someone born with a mutation for degenerative retinal disease, for example, could someday have the mutation edited and repaired before their eyesight begins to fail.

Linda Zangwill, PhD

DIAGNOSIS BY MACHINE

Advancing imaging technologies—including the use of machine learning to interpret images—is being linked to this genetic information. Shiley researchers have been using and helping to refine a technique called optical coherence tomography, which uses light waves to create a picture of a patient's retina. It's a noninvasive test that's easy to administer and can measure the thickness of different layers of the retina, and the arrangement and functionality of blood vessels.

"These technologies have not only revolutionized routine clinical exams, but also research," said Linda Zangwill, PhD, professor of ophthalmology and director of clinical research at Shiley's Hamilton Glaucoma Center. "We can see things we've never seen before."

Using artificial intelligence, machines can be taught to analyze the images and find patterns—some that an ophthalmologist might have spotted, but others perhaps overlooked. Zangwill and colleagues are using the approach to analyze thousands of images collected through DIGS and other studies.

DISEASE IN A DISH

Natalie Afshari, MD

Genetic engineering tools are also being used in combination with stem cell technology.

Karl Wahlin, PhD, assistant professor of ophthalmology, directs the Richard C. Atkinson Laboratory for Regenerative Ophthalmology at Shiley Eye Institute, one of the few labs in the world to grow 3-D stem cell models of human retinas.

Wahlin uses the CRISPR-Cas9 gene-editing tool to introduce mutations into pluripotent stem cells. As those cells develop into a mini-retina with a degenerative disease, it gives researchers the opportunity not only to watch how a genetic mutation manifests in the eye but also to test medications without the time, expense or regulatory hurdles of animal testing or clinical trials. "We'd like to be able to identify drugs that would allow us to reverse the course of disease," Wahlin said.

Wahlin's lab has already used this "disease-in-a-dish" technique to generate models with several types of retinal degeneration, including Leber's congenital amaurosis, an inherited disease that causes severe vision loss in infants.

Genetics and stem cell research have fueled several research advances. For example, Natalie Afshari, MD, professor of ophthalmology and chief of cornea and refractive surgery, and colleagues have identified three new genetic markers for Fuchs endothelial corneal dystrophy (FECD), a corneal disease that can be inherited and is the most common cause of corneal transplants.

Kang Zhang, MD, PhD, professor of ophthalmology and chief of ophthalmic genetics, has published research with colleagues in China about a new approach to remove congenital cataracts in babies and allow remaining stem cells to regenerate new, unclouded lenses.

A PLACE FOR SYNERGY

Since it opened in 1991, the Shiley Eye Institute (originally called the Shiley Eye Center) has been home to numerous entities and enterprises. The Hamilton Glaucoma Center and Joan & Irwin Jacobs Retina Center, for example, debuted there in 2004. The building houses both laboratories for basic research, including stem cell science, and clinical research spaces. The close quarters are conducive to collaboration. Talk to a Shiley researcher long enough and they'll invariably mention the importance of synergy in their work—the crucial exchange of ideas, both with those close at hand and increasingly with scientists, engineers and others across the UC San Diego campus and surrounding mesa.

But they also see a need to grow.

The vision of Weinreb and others is a new five-story facility that would house clinical space, including the latest diagnostic tools and state-of-the-art operating rooms, along with laboratories for vision research and collaboration with other disciplines, space for clinical research, and areas dedicated to education of students, trainees, community physicians and patients.

"The Shiley Eye Institute is leveraging a multidisciplinary approach that integrates vision research, bioengineering, neurosciences, genetics and stem cell biology to treat, prevent and cure blindness," said Weinreb. "We have outgrown our clinical space. A new building will not only provide needed space for patient care, but will bridge the gap between the laboratory and clinic by colocating discovery and translational investigations alongside patient care."

STEM TO STEM

Self-renewing cells promise therapies that span the human body and condition.

By Scott LaFee

> "Some of the things we do now were science fiction when I was an undergrad at UC San Diego more than 40 years ago."
>
> — LARRY GOLDSTEIN, PhD

The therapeutic allure of stem cells is as obvious and as broad as their ability to become almost any kind of tissue. They are the cellular putty of life, and scientists are striving to reshape their powers of differentiation to repair virtually everything that ails us — from restocking blood ravaged by leukemia to rebuilding broken hearts and wounded knees.

That drive is global, but nowhere is it more intense or has progress been more fruitful than at UC San Diego School of Medicine, which has become a hub for both basic stem cell science and for efforts to translate fundamental discoveries into novel clinical therapies.

"Some of the things we do now were science fiction when I was an undergrad at UC San Diego more than 40 years ago," said Larry Goldstein, PhD, director of the Sanford Stem Cell Clinical Center at UC San Diego Health and scientific director of the Sanford Consortium for Regenerative Medicine, a collaborative facility housing like-minded researchers from UC San Diego, La Jolla Institute for Allergy and Immunology, Sanford Burnham Prebys Medical Discovery Institute, the Salk Institute for Biological Studies and The Scripps Research Institute.

Goldstein is arguably the face of local stem cell research. He played a seminal role in the development and passage of Proposition 71 — the local paper dubbed him "the stem cellsman" — in 2004, which established a $3 billion fund for stem cell research and launched the California Institute for Regenerative Medicine (CIRM), the state's stem cell agency.

He continues to be a vocal advocate, but also a working scientist, most notably announcing in 2012 that his laboratory had created unprecedented stem cell-derived models of sporadic and hereditary Alzheimer's disease, using induced pluripotent stem cells from patients with the neurodegenerative disorder.

"It's a first step. These aren't perfect models. They're proof of concept," said Goldstein at the time. But the utility of living, functional Alzheimer's neurons in a dish is undeniable. Researchers can study how these neurons function (or don't) and test different drugs and therapies more quickly and directly — without putting patients at risk.

"We have made profound progress in understanding the basic nature and abilities of stem cells. We know a great deal about how they work and differentiate and, in a number of cases, how to make them become the kinds of cells we think we need."

— LARRY GOLDSTEIN, PhD

Alysson Muotri, PhD

David Traver, PhD

STEM CELL FLAVORS, MINI-BRAINS AND THE CHALLENGES OF CANCER

Stem cells come in different flavors of potency. Embryonic stem cells are pluripotent, able to develop into any kind of cell in the adult body, but their source makes them politically fraught and difficult to use.

Induced pluripotent stem cells (iPSCs), which emerged in 2006, dramatically resolved that dilemma. IPSCs are derived from adult cells—skin cells, for example—that have been reverted back to stem cell status, then reprogrammed to become almost any kind of cell.

In 2010, Alysson Muotri, PhD, professor in the Departments of Pediatrics and Cellular and Molecular Medicine and director of the UC San Diego Stem Cell Program, with colleagues, used iPSCs to create the first cellular model of autism spectrum disorder. A year later, Muotri and collaborators did the same for amyotrophic lateral sclerosis (Lou Gehrig's disease) and in 2016, they used iPSCs to create a model of Williams syndrome, a rare condition characterized by hyper-social predisposition, causing persons to tend to be overly friendly, overly trusting, drawn to strangers and yet anxious. Muotri said he was interested in Williams syndrome because it is so different from autism. Last year, his lab produced the first brain model of anorexia nervosa using iPSCs derived from adolescent females with the eating disorder.

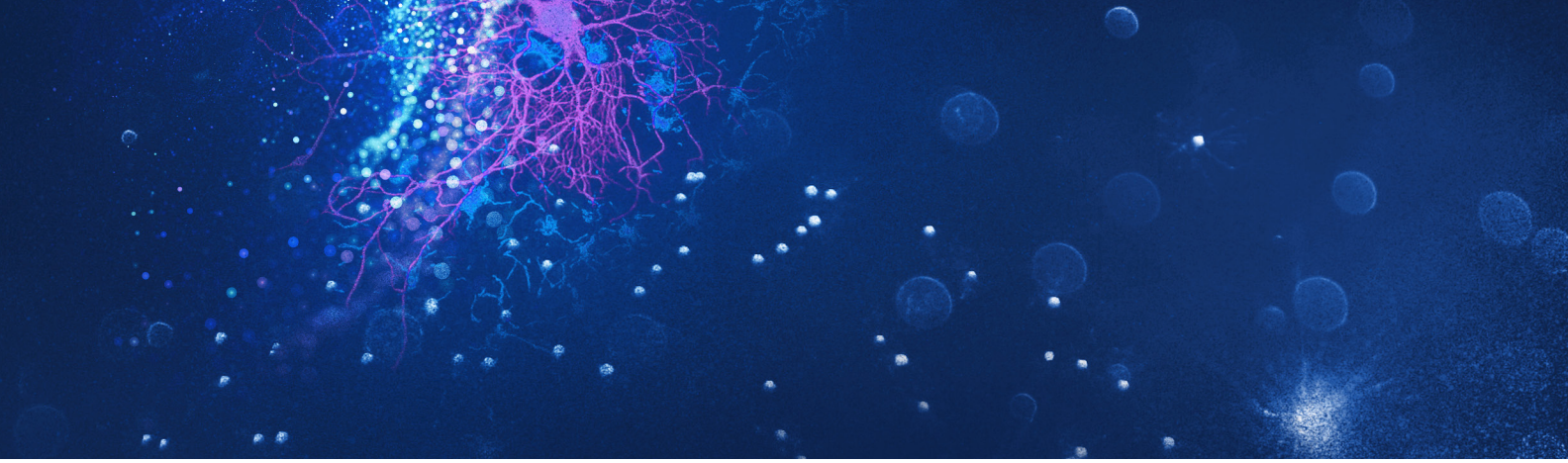
"We have improved our protocols, we can now create human 'mini-brains' from iPSCs," said Muotri. Indeed, he and colleagues have used these 3-D organoid structures to not only study genetic diseases, but also show how the Zika virus causes microcephaly (small brains) in newborn babies by targeting neuron precursor cells that form the brain's cortex.

Stem cells provide researchers with a way to poke and prod at the very foundations of life and the pathologies of disease. David Traver, PhD, professor in the Department of Cellular and Molecular Medicine, and colleagues have identified essential genes and cellular systems critical to the creation of hematopoietic stem cells, which give rise to all blood cell types. Their discoveries have implications for creating stem cell-based therapies for diseases like leukemia.

Not all stem cells are beneficial. Many cancers initially respond well to treatment, seeming to disappear, only to recur later in another part of the body. The spread of cancer, called metastasis, is responsible for 90 percent of cancer-related deaths.

The reason is likely cancer stem cells, first isolated just 24 years ago. They possess similar self-renewing powers, allowing tumors to recover and rebound. Over the last decade, an international team led by Catriona Jamieson, MD, PhD, professor of medicine and director of Stem Cell Research at Moores Cancer Center, has discovered how changes in the environment surrounding a tumor activate specific stem cell genes. They also found these genes can accelerate tumor growth and resistance to therapy.

These discoveries have guided development of several clinical trials targeting activated stem cell pathways in pre-leukemic disorders and leukemia. This successful paradigm shift—targeting self-renewing cancer stem cells that contribute to cancer relapse—underscores the need to find new combination therapies that specifically eradicate cancer stem cells in many cancer types. Jamieson's lab and colleagues are currently pursuing this work with the National Institutes of Health, CIRM, philanthropic and industry funding.



Catriona Jamieson, MD, PhD

Mark Tuszynski, MD, PhD

THE LONG JOURNEY — AND LONGER LEAP — TO HUMAN THERAPIES

The goal of all stem cell research, of course, is to create new, effective treatments or cures. Hype and hope have often clouded reality. "Progress is measured in terms of years and decades," said Goldstein, an ardent critic of proliferating but unproven and unapproved treatments touted by suspect clinics. "How long does it take to achieve a real breakthrough? To actually solve a disease? There's no way to make that prediction. Research is about discovering what you don't know. You can discover something that makes the research go faster or something that makes it go slower. Breakthroughs and setbacks happen constantly."

True success requires dogged effort.

For more than a decade, Mark Tuszynski MD, PhD, professor of neurosciences and director of the Center for Neural Repair, has painstakingly sought a remedy for devastating spinal cord injuries, to literally bridge the divide between pre- and post-injury. In laboratory rats, his team has embedded neural stem cells, mixed with growth factors, at the site of severe spinal cord injuries. The resulting regeneration has been dramatic and functional: The paralyzed animals regain measurable ability to move.

"There is more work to do prior to moving to humans," Tuszynski said. "We must establish long-term safety and long-term functional benefit in animals. We must devise methods for transferring this technology to humans in larger animal models. And we must identify the best type of human neural stem cell to bring to the clinic."

In 2013, businessman and philanthropist T. Denny Sanford committed $100 million to create the Sanford Stem Cell Clinical Center at UC San Diego Health, in part due to work like Tuszynski's. The center is intended to speed translational and transformational stem cell research.

In 2014, the Center was named a CIRM "alpha stem cell clinic," directed by Jamieson. The designation provides extra funding and support to create a clinical hub for first-in-human stem cell-related clinical trials. That same year, UC San Diego researchers did just that, launching three unprecedented trials to investigate 1) a UC San Diego-developed cancer stem cell-targeted treatment, cirmtuzumab, for chronic lymphocytic leukemia, the most common form of blood cancer, 2) a stem cell-based therapy for type 1 diabetes and 3) whether neural stem cells injected at the site of a chronic spinal cord injury can restore connections and at least some motor and sensory function. That last trial, different from Tuszynski's, expanded last year and provided the clinical framework for a new trial for patients with acute cervical spinal cord injury.

"What we are seeing after years of work is the rubber hitting the road," said Goldstein. "We have made profound progress in understanding the basic nature and abilities of stem cells. We know a great deal about how they work and differentiate and, in a number of cases, how to make them become the kinds of cells we think we need. Now we have to put that knowledge to the test in people, for people."

Getting under my Skin

By Heather Buschman, PhD

Let's meet the smallest (and multitudinous) denizens of my largest organ.

Heather Buschman, PhD

IF YOU'RE LIKE ME, you tend to view your skin as a merely cosmetic body part. "Only skin deep," we say, when something is particularly shallow. When I look at my own skin, I see wrinkled hands that remind me of my mother's. I see scars on my face from a bicycle accident.

But Richard Gallo, MD, PhD, chair of the Department of Dermatology at UC San Diego Health, told me that to think of your skin only as the way you look doesn't do it justice.

"Skin is the most seen but least understood organ," he said. "It's how we recognize ourselves as human, and as individuals."

Thing is, our skin is not even as human as we'd like to think. We all have up to 100,000 bacteria living on every square inch of skin, most of which help keep us healthy. The unique genetic makeup of these communities is known as our skin microbiome.

"That's exciting because it means we're not just locked into the genes we inherited from our parents—we can exchange most of our genetic information for something better," Gallo said.

What's living on my forehead

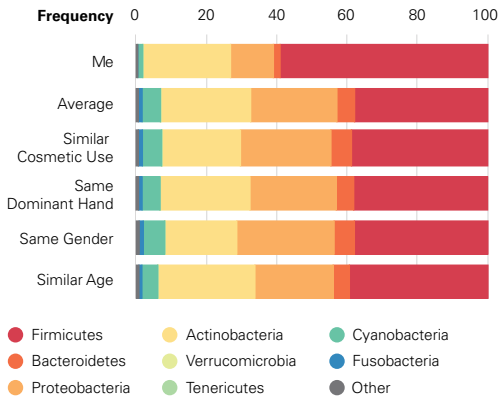
To learn about my own skin microbiome, I turned to the American Gut Project, the world's largest crowdfunded, citizen science project. The name has become a bit of a misnomer as it has grown—it's neither just for Americans nor just to study your gut microbiome. So far, more than 13,000 stool, skin, mouth and a wide range of other samples have been submitted from more than 40 countries.

American Gut is managed by Embriette Hyde, PhD, an assistant project scientist in the lab of Rob Knight, PhD, in the UC San Diego School of Medicine. Knight is director of the UC San Diego Center for Microbiome Innovation, American Gut co-founder, and a pioneer in the field. He helped develop the genetic sequencing technique that allows researchers to identify the kinds of bacteria in hundreds of different samples simultaneously.

To get started, I contributed to the project and received a sampling kit. I swabbed the skin on my forehead and filled out an online questionnaire, which asked things like "How often do you wear cosmetics?" (daily) and "Do you live with pets?" (yes, cats). Then I mailed my sample back to Hyde and team. They sequenced a bacterial gene called 16S rRNA, which acts as a microbial "fingerprint" to provide information about the microbes in a sample.

Turns out I have more Firmicutes on my skin than the average American Gut participant. Firmicutes are a group of bacteria that includes *Streptococcus* and *Staphylococcus,* commonly found on skin. Together, these two types made up almost 50 percent of all bacteria in my sample.

"We don't yet know why your skin microbiome is skewed that way, or what it might mean for your health," Hyde explained. "But now your microbial data—paired with your lifestyle information—are part of a database. So scientists around the world can use this information to help answer questions like how the things you eat, cosmetics you use or other lifestyle factors might be associated with different disease states. For example, researchers are investigating how eating fermented foods influences a person's gut microbiome, or how certain oral microbes are linked to migraines."



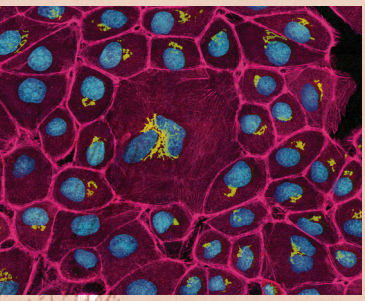
Makeup of my skin microbiome
This graph shows the types of bacteria living on my forehead, the relative amounts of each, and how that compares to other American Gut participants. I have more Firmicutes (red) than most.

The problem with antibiotics

Once I had a clearer picture of my microbial companions, I wanted to learn how to take better care of them. Let's start with hygiene.

Obviously, advances in hygiene in the past century have reduced deaths during childbirth and from dysentery and other infections. Today, kids at my daughter's school go everywhere with hand sanitizer bottles attached to their backpacks. But how clean is too clean?

As you might guess from the title of their 2017 book *Dirt is Good*, Knight and co-authors say we should minimize the unnecessary use of hand sanitizer and antimicrobial soaps. Instead, they want more kids to visit farms, garden and play with pets.



Epithelial skin cells
Image by Thomas Deerinck, NCMIR, UC San Diego

Their advice is prompted by what's known as the "hygiene hypothesis"—the idea, now well-supported by research, that lack of exposure to microbes in the typical Western, urban lifestyle leaves our immune systems inadequately trained to know the difference between things they should and shouldn't attack. Our city-dwelling immune systems are literally attacking our own molecules and silly stuff like pollen because they don't know any better. As a result, Knight said, we see much higher rates of allergies, asthma and autoimmune diseases in "hygienic" cities than in farming communities and developing countries.

More recently, the hygiene hypothesis has been updated to the "old friends" hypothesis—the idea that rather than more exposure to pathogens (risky, obviously), what we really need is exposure to more "friendly" bacteria. We can do that by following Knight's recommendation to get dirty.

Old friends and ninjas

While bacterial exposures are often good, sometimes we do need to get rid of pathogenic bacteria. We typically do that by taking antibiotics. But antibiotics are not specific to the one type of bacteria that's making me sick. That not only hurts my healthy microbiome, but incidental antibiotic exposure favors antibiotic-resistant bacteria—fast becoming a global health crisis.

When I'm sick, how can I kill bad microbes, but still spare those "old friends"?

Victor Nizet, MD, professor of pediatrics at UC San Diego School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences, has an idea. To explain, he compares bacterial infections to a home robbery, and your immune system to a ninja.

"If your home is usually protected by a ninja, but a thief breaks in while he's momentarily napping, it makes more sense to just wake up the ninja, rather than call in a SWAT team, hoping they'll arrive in time and get the job done without wrecking your house," he said.

Instead of focusing solely on killing the bacteria (home invaders) with a SWAT team (antibiotics), Nizet and team are testing ways to boost the immune system (ninja) so it can better fight the infection on its own. In one study, they found that the breast cancer drug tamoxifen triggers immune cells to release more "nets." With tamoxifen, the immune cells captured more pathogenic bacteria, and infected mice lived longer.

Microbes as medicine

Gallo has a different approach to killing specific bad bacteria without harming the good: Enlist friendly microbes.

He thinks this might be a promising way to help people with eczema. This skin condition, which can affect 22 percent of children under age 5 in industrialized countries, is characterized by itchy, scaly patches of skin. People with eczema have more of the bacterium *Staphylococcus aureus* on their skin than most, which exacerbates the problem.

"In people with healthy skin, resident bacteria produce natural antibiotics that kill *S. aureus,*" Gallo said. "But in eczema, we find fewer of these helpful bacteria."

Gallo and team wondered if simply giving people with eczema more *S. aureus*-fighting bacteria might help. To test this, they isolated the few beneficial bacteria they could find on the skin of people with eczema. Then they turned that into personalized skin creams that they gave back to the affected individuals.

"We were surprised to see 100-fold reductions in *S. aureus* after a single application," Gallo said. "While we've only tested this in five volunteers so far, it has worked for every one of them."

According to my American Gut results, I have a lot of *Staphylococcus* on my forehead. Yet I don't have eczema. It's likely that the *Staphylococcal* bacteria I carry are not the troublesome *Staphylococcus aureus* variety, but a more beneficial type known as *Staphylococcus epidermidis*.

In any case, lots more work has to be done before we might see probiotic skin creams or other microbiome-related therapeutics on drugstore shelves. But if the microbes on our skin—to say nothing about those in our guts and mouths—are that powerful, I can't help but wonder… have we humans evolved simply to serve them?

Whatever the answer, for now I think I'll hedge my bets and try to make nice with my tiny overlords.

SEEING IS UNDER-STANDING

The many ways we see cells under a microscope or a patient in the operating room have changed dramatically in 50 years ... and continue to evolve.

By Heather Buschman, PhD

In the 1980s and '90s, Roger Tsien, PhD, at UC San Diego School of Medicine and three colleagues on the other side of the country made the invisible visible. Osamu Shimomura, PhD, had long studied bioluminescent jellyfish at the Marine Biological Laboratory in Woods Hole, Mass., and first identified the green fluorescent protein (GFP) that helps it glow. Douglas Prasher, PhD, also working at Woods Hole at the time, then isolated the gene that encodes GFP. Prasher sent the gene to Martin Chalfie, PhD, at Columbia University, who used it to illuminate human and other cells.

Prasher also sent the GFP gene to Tsien, who took their work a step further. Combining his skills in chemistry and biology with new genetic engineering technologies, Tsien found ways to tweak GFP's makeup, making it glow more brightly and consistently. Then he created a full-color palette of fluorescent proteins that scientists could use to track different cellular processes at the same time. He then used different color combinations that can report changes in a specific molecule's concentration and location within cells.

Roger Tsien, PhD

Learning from Nature
Tsien and collaborators discovered and developed green fluorescent protein (GFP), derived from the jellyfish *Aequorea victoria*, into an indispensable research tool.

GFP and its rainbow of cousins with names like mCherry and mOrange quickly became indispensable tools in life science labs around the world, allowing researchers to look into cells or whole animals, to watch molecules interact in real time and ask questions once thought impossible to answer.

"Our work is often described as building and training molecular spies," Tsien once said, "molecules that will enter a cell or organism and report back to us what the conditions are, what's going on with the biochemistry, while the cell is still alive."

In 2008, Tsien, Shimomura and Chalfie were awarded the Nobel Prize in Chemistry. The Nobel committee highlighted a few of GFP's many applications, such as tracking the development of Alzheimer's disease in the brain or the growth of pathogenic bacteria.

As professor of pharmacology, chemistry and biochemistry at UC San Diego School of Medicine, Tsien continued his research, mentored students and postdoctoral trainees, and taught classes for 27 years.

When he died in 2016, social media literally illuminated in his memory, with scientists around the world posting images of cells glowing in his honor.

Tsien's legacy lives on. His work forms the basis for untold numbers of laboratory and clinical technologies and discoveries.

Two described here are ongoing at UC San Diego School of Medicine—an effort to make surgeries safer and more precise, and laboratory studies of how memories are stored in the brain.

Enlightened surgery

Surgeons often rely on feel, look and experience to tell if they have removed all of a tumor, while sparing healthy tissue and nerves. Unfortunately, this inexact approach means tumor tissue is sometimes missed, increasing the chances that the malignancy will reoccur and the patient will require further treatment. In some cases, incidental nerve damage during surgery can cause weakness, pain or even paralysis.

To see if they might be able to make surgery safer and more effective, Tsien teamed up with Quyen Nguyen, MD, PhD, head and neck surgeon at Moores Cancer Center at UC San Diego Health. Over 13 years of collaboration, they developed injectable fluorescent molecules that specifically light up tumors and hard-to-see peripheral nerves.

Here's how the tumor-labeling molecule works: First, the molecule is U-shaped and comprises three parts. The first is a positively charged polycation, which sticks to every tissue. The second is a negatively charged polyanion, which is non-sticky and so acts like the back of a sticker. The third is a cleavable link that can only be cut by the right enzyme in the body, which acts like very specific molecular scissors.

When the three-part dye hits normal body tissue, nothing happens. But cancer cells have molecular scissors that snip the link, removing the backing from the sticker and causing the tumor to radiate with fluorescent dye.

"The cool thing about this fluorescence is not just that it's bright, but that it can go through tissue, so you can see a tumor even if it's buried deep," Nguyen said. "Cancerous tissue just glows, right there in the operating field."

Quyen Nguyen, MD, PhD

Tsien, Nguyen and colleagues also screened thousands of small peptides (amino acid chains, like those that make up proteins) for those that preferentially bind peripheral nerve tissue in mice. They labeled the most promising candidate with a fluorescent tag and found that it creates a distinct contrast—up to tenfold—from adjacent non-nerve tissues. The effect occurs within two hours and lasts for six to eight hours, with no observable effect on nerve activity or animal behavior.

This fluorescence labeling works even in nerves that have been damaged or severed, as long as they retain a blood supply. In other words, fluorescence labeling might be a useful tool in future surgeries to repair injured nerves.

"The analogy I use is that when construction workers are excavating, they need a map showing where the existing underground cables are actually buried, not just old plans of questionable accuracy," Tsien said in 2011. "Likewise, when surgeons are taking out tumors, they need a live map showing where the nerves are actually located, not just a static diagram of where they usually lie in the average patient."

So far, these fluorescent probes have only been tested in rodents. But Nguyen and team are rapidly translating their discoveries into the clinic. First, they found and optimized a novel peptide version that specifically labels nerves in human tissue samples. Then she and colleagues started a company, Alume Biosciences, to license the nerve-lighting technology from UC San Diego. They are currently conducting the pharmacology and toxicology tests required by the U.S. Food and Drug Administration before they can initiate a clinical trial. Their first test will be in patients with salivary gland tumors undergoing surgery where the facial nerve is at risk for inadvertent injury.

"If all goes smoothly," Nguyen said, "we could begin testing these nerve-labeling fluorescent probes on human facial nerves in late 2018."

Revealing memories

While Nguyen's team uses Tsien's fluorescent technology to see better with the naked eye, his probes also make it much easier to see cells and their components under microscopes.

"Microscopy evolved as labeling methods evolved," said Mark Ellisman, PhD, professor of neurosciences and bioengineering. Ellisman joined the UC San Diego School of Medicine faculty in 1977. In 1988, he founded what is now the National Center for Microscopy and Imaging Research (NCMIR). Supported by the National Institutes of Health, NCMIR is now the go-to place for researchers around the world who want to develop and apply microscopy techniques to look at cellular life at just about any scale.

Surgery in Technicolor
In a mouse model, injectable fluorescent peptides make hard-to-see peripheral nerves glow, alerting surgeons to their location and extent. *Left:* mouse nerves without fluorescent labeling. *Middle and right:* labeled mouse nerves.

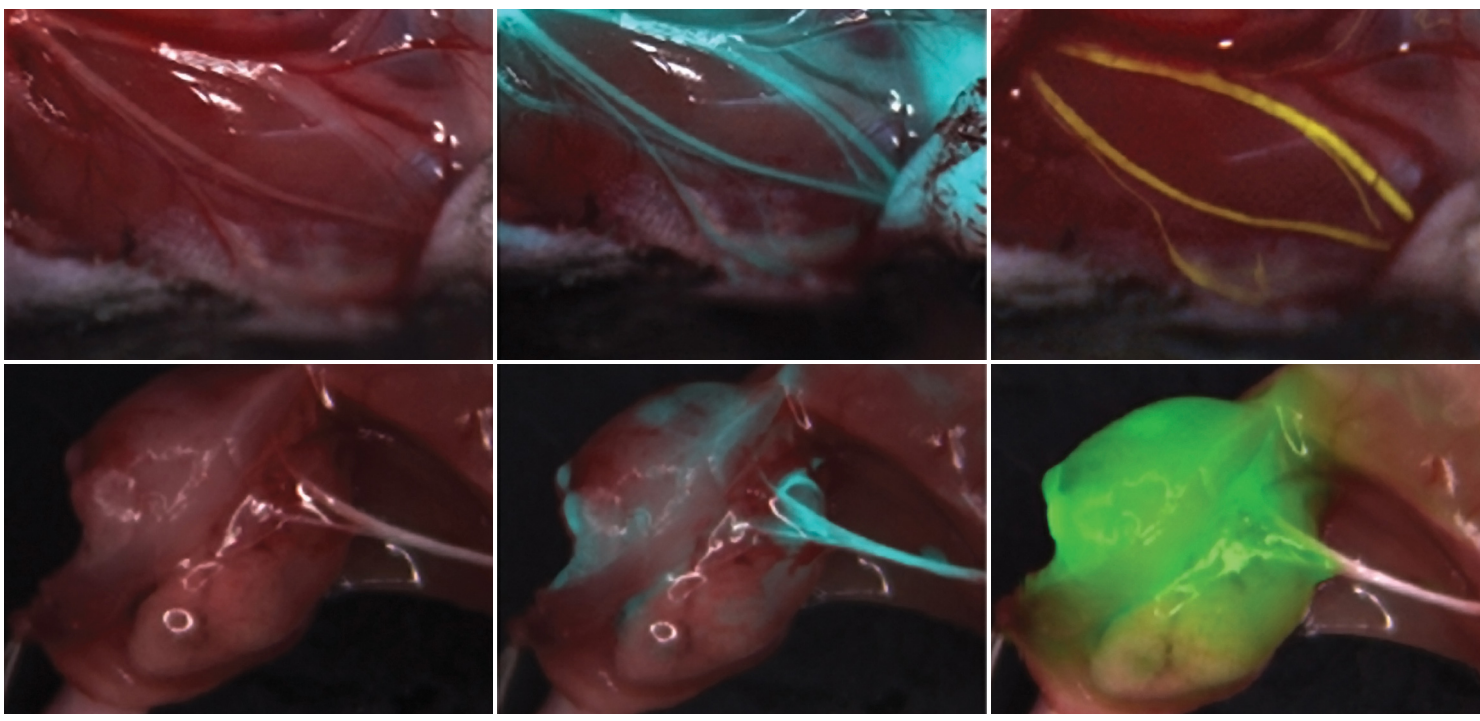


Photo by Kyle Dykes

National Center for Microscopy and Imaging Research (NCMIR) at UC San Diego, 2017
John S. O'Brien, MD (inset left), professor and second chairman of the Department of Neurosciences, who discovered the genetic cause of Tay-Sachs disease and developed the first tests for the disorder, with the first electron microscope at UC San Diego School of Medicine, donated by Ernest W. Mandeville (right) in 1970.

Mark Ellisman, PhD

At NCMIR, you can find more microscopic views than anywhere else in the world. That's in part because Ellisman and NCMIR scientists are microscopy pioneers. Their facility houses approximately $100 million worth of technology, including electron microscopes, analytical microscopes, even robots that can slice sections of tissue and scan them continuously over weeks to construct 3-D images.

These microscopes don't exactly just come straight from a factory floor. NCMIR staff are constantly building and tinkering to improve them, often contracting with manufacturers. As a result, many of their microscopes are one of a kind.

"The first thing we do when we get a new scope is pop open the hood and fix it up," Ellisman said. "In many ways, NCMIR is like a specialty garage that soups up muscle cars for maximum performance."

One room-sized microscope, for example, has a hole cut in the back and an additional lens added—a lens made by the same company that made the corrective optics to fix the Hubble telescope. The scope can provide resolution down to one angstrom, the size of one hydrogen atom.

"But we're not just interested in the technology, we also want to understand how the biology works," Ellisman said.

To this end, NCMIR takes on an average of 100 projects per year, working with researchers interested in everything from HIV to cancer.

With NCMIR technology, researchers can watch how tumor cells migrate, right down to the whiskers on an individual cell's molecular feelers or "arms" as it reaches and spreads, and how that cell responds to drugs.

According to Ellisman, they pick projects where there is a gap in knowledge. Then the team determines how to further advance probe technology, enhance microscopes, or apply a series of microscopies, to answer the question.

For years, one question has tenaciously nagged at biologists and researchers like Tsien: How are lifelong memories stored?

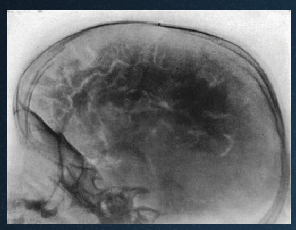
Shortly before he died, Tsien and his team were working with Ellisman and NCMIR colleagues to find an answer. They wanted to visualize and understand previously underappreciated structures in the brain called perineuronal nets. These nets encase synapses, the structures through which neurons communicate. Tsien believed perineuronal nets play a role in how we store lifelong memories.

One clue is that while many proteins in the body turn over regularly, recent findings by the group show that perineuronal net components are surprisingly long-lasting. Stable isotope labeling experiments and visualization with NCMIR's advanced electron microscopes and ion microscopes elsewhere are revealing new details about these nets. They may stick around for a mouse's entire life, as Tsien postulated. And during that time, synapses may form through the net holes, establishing stability and retaining long-term information.

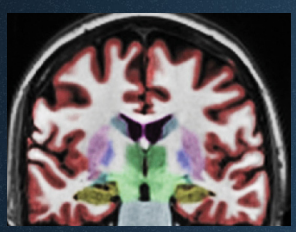
Remaining members of Tsien's team and NCMIR researchers are now continuing their quest to track how fluorescently labeled perineuronal nets change over time and appear under a variety of conditions, including those that occur in the aging brain.

"This was Roger's vision, and we're dedicated to carrying it on," Ellisman said.

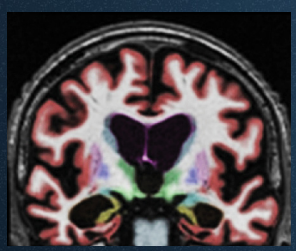
Brain Gain
Our ability to visualize the brain has advanced dramatically over the decades—from vague shapes and shadows to highly detailed structures and cells.



Human brain visualized by pneumoencephalography, early 1900s.



Healthy brain viewed by volumetric MRI, 2017.



Brain with Alzheimer's disease, as evidenced by the severe loss of tissue and the fluid taking up the space where tissue was lost, 2017.

Picturing Alzheimer's Disease

When the UC San Diego School of Medicine admitted its first class in 1968, the most common way to look at the brain of a living person was a technique known as pneumoencephalography. It was a painful procedure that required a lumbar puncture, draining most of the patient's cerebrospinal fluid from around the brain and replacing it with air. That way the brain would show up more clearly on a simple X-ray. But pneumoencephalography images couldn't directly reveal abnormalities, such as a tumor or degeneration. A radiologist reading them could only tell if the shape or location of air-filled structures had been altered.

Fortunately, pneumoencephalography was superseded by CT and MRI scans in the late 1970s and early 1980s. MRI, short for magnetic resonance imaging, is not only non-invasive, it provides much greater resolution of the brain.

"Looking at an MRI of a brain is like opening the top of the skull and looking right at the tissue," said James Brewer, MD, PhD, chair of the Department of Neurosciences and interim director of the Shiley-Marcos Alzheimer's Disease Research Center at UC San Diego School of Medicine.

He would know. Brewer has likely seen more brains with Alzheimer's disease using MRI than anyone else in the world. His ultimate goal is to use MRI to diagnose this neurodegenerative disease in a way that's noninvasive, allowing for earlier detection and intervention.

Right now, diagnosing Alzheimer's disease is not easy. Until recently, doctors couldn't be sure a person had Alzheimer's until the patient died, and an autopsy revealed signature amyloid and tau protein deposits in the brain. Even today, Alzheimer's diagnosis relies on a detailed patient history and brief cognitive function tests that measure how well the patient performs a wide variety of skills. These tests are improving, but they're still subjective and don't reveal much until the disease is advanced.

That's why Brewer and team are developing "volumetric" MRIs that measure a patient's degree of neurodegeneration. They are applying machine learning algorithms to detect patterns of neurodegeneration that allow them to distinguish Alzheimer's disease from what normal brain atrophy looks like in a 60-, 70- or 80-year-old person.

"We've scanned thousands of brains of healthy patients across every age to get a baseline," Brewer said. "Then we developed quantitative measurements for objective readouts of what's normal and what's not. Much like a pediatrician's growth curve, we can now tell a patient how the size of his or her hippocampus memory structure is compared to healthy individuals of the same age, gender and head size."

While not common everywhere in the U.S., volumetric MRI is a regular part of clinical practice at UC San Diego Health.

Volumetric MRI may not be the only path to early Alzheimer's detection. Researchers are also developing ways to label amyloid and tau proteins in living brains and detect telltale biomarkers in a patient's cerebrospinal fluid.

"We're getting closer and closer to detecting Alzheimer's disease years before symptoms appear," Brewer said. "But that's both a blessing and a curse. It's a blessing because early detection means we can intervene before neurodegeneration causes irreversible cognitive loss. The curse is we don't currently have a drug to stop Alzheimer's disease."

In any case, Brewer is amazed at the imaging advances that have been made in a single lifetime, and especially in the past five years.

"I'm just glad we don't stick air in people's cerebrospinal fluid anymore," he said.

RNA: THE OTHER BUILDING BLOCK OF LIFE

By Heather Buschman, PhD

DEOXYRIBONUCLEIC ACID, or more commonly DNA, is the fundamental building block of life. We are just beginning to see the implications of genomic sequencing and gene editing with promising techniques, such as CRISPR-Cas9. But many diseases, including cancer and autism, are linked to problems with another fundamental biological molecule—RNA.

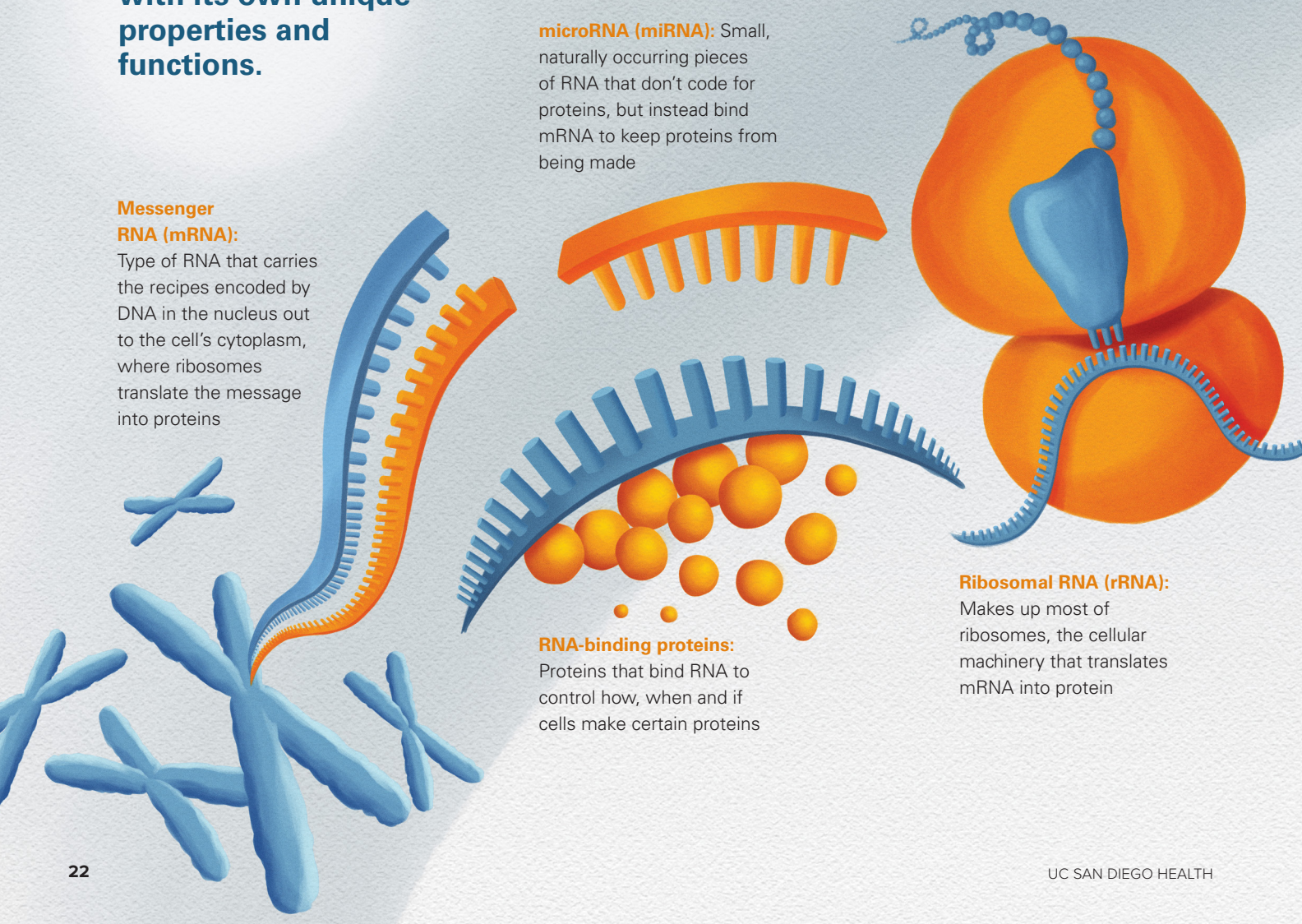
While DNA is like the architect's blueprint for a cell, RNA is the engineer's interpretation of the blueprint. In the central dogma of life, DNA in the nucleus is transcribed into RNA, RNA carries the message out into the cytoplasm, and enzymes called ribosomes translate RNA to make proteins.

But it's not always so straightforward. Cells frequently modify RNA as a means to control which proteins are made and when. And RNA is frequently flawed in cancer and other diseases. In contrast to humans, the entire genomes of some viruses, including Zika and HIV, are made up of RNA instead of DNA. These viruses hijack their human host's cellular machinery to translate their RNA into proteins.

There are many types of RNA, each with its own unique properties and functions.

microRNA (miRNA): Small, naturally occurring pieces of RNA that don't code for proteins, but instead bind mRNA to keep proteins from being made

Messenger RNA (mRNA): Type of RNA that carries the recipes encoded by DNA in the nucleus out to the cell's cytoplasm, where ribosomes translate the message into proteins



RNA-binding proteins: Proteins that bind RNA to control how, when and if cells make certain proteins

Ribosomal RNA (rRNA): Makes up most of ribosomes, the cellular machinery that translates mRNA into protein

Here is a peek at just a few of the ways UC San Diego School of Medicine researchers are studying — and exploiting — RNA and unraveling its role in human development and health.

Mutations in RNA-binding proteins can scramble RNA, leading to Lou Gehrig's disease (ALS)
Led by Gene Yeo, PhD, professor of cellular and molecular medicine

"These findings may have important implications for researchers who are targeting RNA as a means to treat many neurological diseases."

The body's own RNA editing enzymes generate leukemia stem cells
Led by Catriona Jamieson, MD, PhD, professor of medicine and chief of the Division of Regenerative Medicine

"We not only found that cancer stem cells co-opt an RNA editing system to clone themselves, we also found a way to dial it down."

mRNAs can be used to distinguish ovarian cancer cells from normal cells
Led by Kelly Frazer, PhD, professor of pediatrics and director of the UC San Diego Institute for Genomic Medicine

"We built a customized computer program to develop an ovarian cancer detection test based on tumor-specific mRNA — setting the stage for early diagnosis and personalized treatments."

Chemical disguise for RNAi drugs helps them slip inside cells to fight cancer and viral infections
Led by Steven Dowdy, PhD, professor of cellular and molecular medicine

"We developed new RNA backbone chemistry and synthesized a 'Trojan Horse' RNAi therapeutic to help with delivery into cells."

RNA-based drugs can help make gene editing more precise
Led by Don Cleveland, PhD, Distinguished Professor and chair of the Department of Cellular and Molecular Medicine

"We are silencing disease-causing genes in the nervous system using designer RNA drugs to transiently manipulate genes with the CRISPR-Cas9 gene editing system."

Zika virus modifies human and viral RNA, influencing viral replication and the human immune response
Led by Tariq Rana, PhD, professor of pediatrics

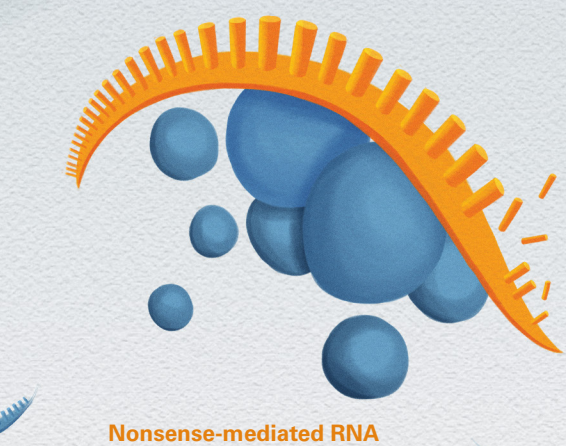
"We are now developing small molecules to target specific RNA structures as a means to treat Zika virus infections."

Brain disease can be caused by defects in an RNA decay pathway
Led by Miles Wilkinson, PhD, professor of reproductive medicine

"Gene mutations that affect the nonsense-mediated RNA decay pathway can lead to intellectual disability and neurodevelopmental disorders."

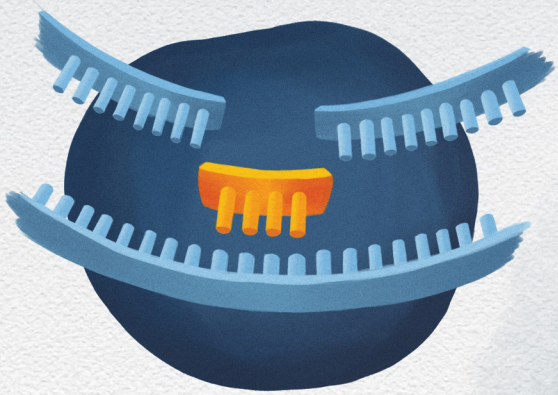
Sequencing 16S rRNA to quickly identify thousands of bacterial species living in a mixed sample
Led by Rob Knight, PhD, professor and director of the Center for Microbiome Innovation

"We're finding new ways to see the trillions of microbes that inhabit our bodies, understand how they change in disease, and leverage them to improve human and environmental health."



RNA interference (RNAi): Normally occurring process that researchers can take advantage of to selectively inhibit production of proteins that cause disease when overproduced or mutated

Nonsense-mediated RNA decay: System cells use to degrade errant mRNAs that encode bad proteins, as well as normal mRNAs that just aren't needed



16S rRNA: Type of rRNA found only in bacteria; sequence is unique for each type of bacteria

Time Tells

By Scott LaFee

In autism research and treatment, earlier is always better.

IT WASN'T LONG AGO that autism seemed to appear without warning, dramatically altering a young child's development and personality.

People searched for a cause, blaming everything from parenting to vaccines. But the true causes of autism have proven to be both more profound and prosaic—a combination of genetics, underlying medical problems and environmental factors, such as viral infections and likely other agents still to be implicated.

Autism—or more broadly, the group of developmental conditions called autism spectrum disorder (ASD)—is complicated, but as its pathology is teased apart, one thing seems obvious: Timing may be everything, both in understanding how and when ASD develops and in treating it.

Few places are better situated to achieve these goals than UC San Diego School of Medicine. For years, scientists here have pursued the telltale clues of ASD. They discovered autism begins in the womb, long before the first clinical signs. They created the "disease in a dish." They found new ways to identify the youngest toddlers at risk, and brain changes involved in social and language symptoms. They are leaders in the effort to unmask ASD.

More than 50 genes have been linked to ASD, but the full number is likely in the hundreds.

Karen Pierce, PhD

"AUTISTIC NEURONS" AND MINI-BRAINS

ASD is a human condition. Animal models exist, typically mice whose brains or behaviors have been modified to mimic ASD, but they do not fully replicate the disorder. "Mice are not tiny people," said Alysson Muotri, PhD, professor in the Departments of Pediatrics and Cellular and Molecular Medicine, director of the UC San Diego Stem Cell Program and a member of the Sanford Consortium for Regenerative Medicine.

Muotri has created other ways to pierce the ASD veil. In 2010, he and colleagues used induced pluripotent stem cells from patients with Rett syndrome, a neurological disorder, to create functional "neurons" that provided the first human cellular model for studying this rare disorder. This opened an avenue for studying autism in a similar way.

"We can now look for and test therapies and see what happens at a cellular level," said Muotri. "This is a fast track to novel treatments."

Last year, Muotri's lab went a step further, producing a "mini-brain" of ASD, derived from people with a particular form of the disease. The new feat revealed a defective molecular pathway during brain development that results in neuronal overgrowth and dysfunction.

THE ROLE OF GENES

In 2014, Eric Courchesne, PhD, professor in the Department of Neurosciences and co-director of the UC San Diego Autism Center of Excellence, and collaborators published a study with clear, direct evidence that ASD begins during pregnancy.

They analyzed 25 genes in postmortem brain tissue of children with and without autism. These included genes that serve as biomarkers for brain cell types, genes that are implicated in ASD and several control genes.

"We discovered patches of disrupted development of these cortical layers in the majority of children," said Courchesne. "Key genetic markers were absent in brain cells in multiple layers that form in the second trimester."

A year later, they underscored ASD's prenatal nature with a study that described for the first time how abnormal gene activity in cellular systems that control brain cell production might underlie the characteristic early brain growth in children with ASD.

"The findings help explain why there are abnormal numbers of brain cells in autism, why the brain grows abnormally too large or too small in some ASD toddlers," he said.

More than 50 genes have been linked to ASD, but the full number is likely in the hundreds. In a 2016 paper, Jonathan Sebat, PhD, associate professor of psychiatry and cellular and molecular medicine and director of the Beyster Center for Genomics of Psychiatric Disease, sequenced the genomes of hundreds of families, each with one child affected by ASD.

They uncovered a surprisingly diverse number of gene alterations that appear spontaneously in offspring and are due to a mutation in a father's sperm or a mother's egg.

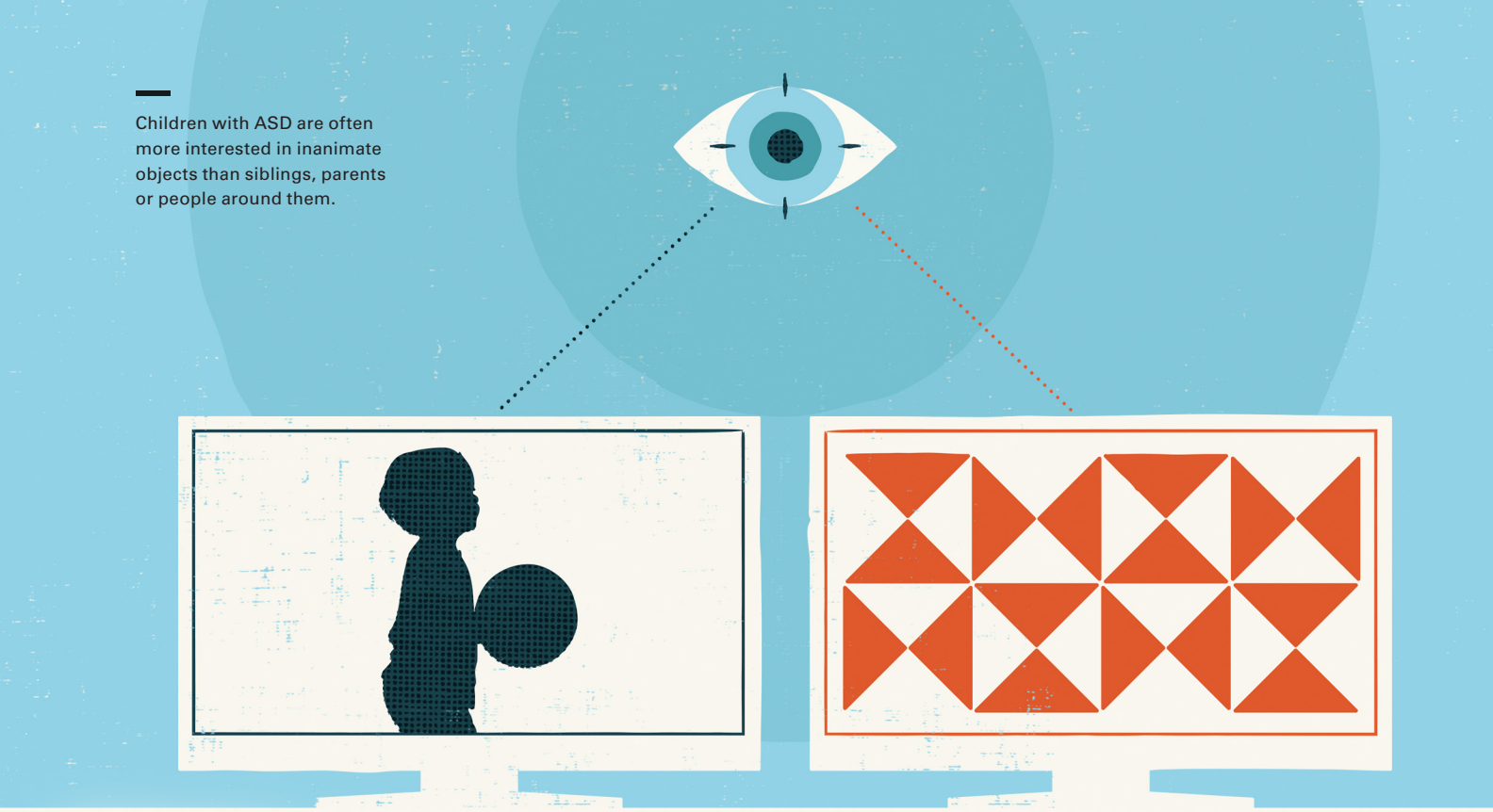
"These mutations occurred at a surprisingly high rate: 20 percent," said Sebat. "Children with autism do not have more mutations overall, but their mutations are more likely to disrupt genes involved in brain development."

Finding and describing all of the relevant mutations of ASD is a monumental task.

"One of the major challenges in autism genetics research is sample size," said Karen Pierce, PhD, professor of neurosciences and co-director of the UC San Diego Autism Center of Excellence. "Individual projects may fail to find genetic abnormalities, not because they aren't there, but because too few people are involved."

A remedy could start with SPARK, the largest autism study ever undertaken in the United States. Sponsored by the Simons Foundation Autism Research Initiative and launched last year, SPARK will collect information and DNA from 50,000 individuals, ages 3 to 60, with ASD. Pierce is one of the study's co-investigators.

These mutations can insert, delete or, in some cases, scramble the DNA sequence.



Children with ASD are often more interested in inanimate objects than siblings, parents or people around them.

INSIDE THE BRAINS OF CHILDREN

Disrupted brain development manifests itself in many ways. In a study using functional magnetic resonance imaging (fMRI) of sleeping toddlers, Courchesne, Pierce and colleagues measured how well their brain hemispheres "synced." Language skills involve regions on both sides of the brain, and syncing strengthens combined functioning, like two connected light bulbs glowing more brightly.

The scientists found that connections between brain hemispheres in children with ASD were significantly weaker in areas responsible for communication skills. "Many things need to be set up right during brain development to enable normal sync between brain areas," said Courchesne. "Brain wiring needs to be right, and the neurons within each area need to send and receive messages in a timely and accurate way."

Courchesne has also used fMRI to predict future language development in ASD. His team looked at how the brain responded to speech in 1- and 2-year-olds at risk for ASD, and followed up with comprehensive, longitudinal assessments of language at ages 3 to 4 years. They found that those with ASD who had weak fMRI responses to speech at 1 to 2 years had poor language outcomes later. Those with ASD who had strong fMRI responses to speech at 1 to 2 years had good outcomes later. This shows that at very early ages it is possible to tell which ASD infants may have better or worse clinical prognoses and opens new avenues for developing early treatments for each subtype of ASD.

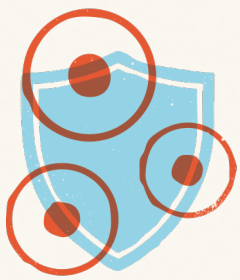
By identifying different brain regions that link to different language outcomes, the researchers say they've advanced both ways to identify the causes of ASD and how best to treat it.

SOONER IS BETTER

The earlier the diagnosis and treatment, the more likely ASD's most compelling characteristics—loss of language and social skills—can be prevented. While Courchesne and others are working on a blood-based genomic marker, the most effective way right now to identify ASD involves well-trained physicians and experts conducting multiple assessments. Pierce is trying to simplify the process along two tracks.

Children with ASD are often more interested in inanimate objects than the people around them. Pierce is using this predilection as a tool to detect ASD in toddlers before they've even begun to speak. Sitting on a parent's lap, toddlers watch a split-screen monitor: one half depicts children playing, the other half shows changing geometric patterns. An infrared camera records the child's eye movements, measuring the amount of time they examine each side.

Typical toddlers focus on the images of other children at play. But in multiple studies, Pierce and collaborators have found that a particular subtype of ASD toddler more often watches the geometric patterns. Among these toddlers who strongly prefer the patterns, Pierce said almost all are subsequently diagnosed with ASD.



"Cells behave like countries at war. When a threat begins, they harden their borders. They don't trust their neighbors."

— ROBERT NAVIAUX, MD, PhD

> "...if (your baby) looks at such moving geometric patterns for long periods of time, but not at fun, social images, you might want to check for other early warning signs of autism."
>
> — KAREN PIERCE, PhD

"If your baby occasionally enjoys looking at the screensaver on your computer, it's no cause for alarm," said Pierce. "But if he looks at moving geometric patterns for long periods, but not at fun, social images, you might want to check for other early warning signs of autism."

ASD symptoms frequently appear before parents recognize something may be wrong. Pierce is leading an effort to identify children with ASD earlier using a one-page checklist that parents fill out at their child's 1-year well-baby visit to the pediatrician.

The project began modestly by testing a checklist of communication behaviors that might indicate ASD among a handful of children. It expanded to include participating pediatricians throughout San Diego County, and now more than 60,000 1-year-olds have been screened. Toddlers whose checklist scores raised concerns received additional evaluation and treatment if an ASD diagnosis was likely.

Since 2011, the checklist has been refined and expanded to other cities, supported by the National Institute of Mental Health. "When I started in the field 25 years ago, children with autism were not identified or helped until they were 4, 5 or even older," said Pierce. "Nobody thought autism was easily treatable, let alone curable. Today, most clinicians have the opposite feeling: There is a significant chance of improvement, especially with early diagnosis and treatment."

AUTISM AND A 100-YEAR-OLD DRUG

For Robert Naviaux, MD, PhD, professor of medicine, pediatrics and pathology, improvement starts at the cellular level. Naviaux believes metabolic dysfunction within cells is a fundamental driver of ASD. Metabolism comprises the chemical and physical processes that maintain life. Cells project a halo of metabolites (molecules involved in metabolism) that broadcast their state of health.

When they are threatened by pathogens, physical forces or toxins, cells respond defensively: Their membranes stiffen. Internal metabolic processes are altered, most notably mitochondria—cells' "power plants." Communication between cells is dramatically reduced.

Naviaux calls this the "cell danger response," and if it persists, impairment can be lasting. If it occurs during childhood, neurodevelopment is delayed.

"Cells behave like countries at war," said Naviaux. "When a threat begins, they harden their borders. They don't trust their neighbors. But without constant communication with the outside, cells begin to function differently. In the case of neurons, it might be by making fewer or too many connections. One way to look at this related to autism is this: When cells stop talking to each other, children stop talking." Even gene mutations can cause cell stress that activates the cell danger response. Naviaux believes that the metabolic syndrome caused by the cell danger response might be a treatable target in many forms of autism.

It's an idea that has drawn considerable attention with the dramatic potential of an old-is-new remedy: a century-old drug called suramin originally developed to treat trypanosomiasis, or sleeping sickness. In animal models of autism, Naviaux found that a single dose shut down cell danger response, reset cellular communications and restored normal behavior.

A phase I/II randomized clinical trial to investigate the drug's safety in 10 boys ages 5 to 14 with ASD produced comparable results. A single low dose was associated with improved scores in language and social interaction, and reduced repetitive behaviors. At low dosage, suramin produced no safety concerns, though Naviaux is quick to note that it is not yet approved for treatment of autism. Larger trials at multiple sites over several years are required to determine whether suramin—or a modern-day analog—is a safe and effective remedy for ASD.

Only time will tell.

Language skills involve regions on both sides of the brain, and syncing strengthens combined functioning, like two connected light bulbs glowing more brightly.

Robert Naviaux, MD, PhD

Give & Make

A short supply of donor organs has required innovation in abundance.

By Michelle Brubaker

ON JANUARY 8, 1968, the *Evening Tribune* reported that "the field of human organ transplantation will arrive in San Diego with the opening of a transplant unit at the County University Hospital." Within a month, the community hospital, operated by UC San Diego, performed the region's first kidney transplant on a 32-year-old aircraft worker.

Marshall Orloff, MD, then chair of the Department of Surgery, declared the transplant surgery to be a success, but warned many future patients would not fare as well. There would not be enough donor kidneys.

His prediction was right. In the following decades, thousands of patients nationally would not survive the wait list for a healthy donated organ.

Each day, 20 Americans die waiting for transplants of kidneys, livers, hearts and lungs. Someone new is added to a wait list every 10 minutes. More than 120,000 adults and children are currently on transplant wait lists. Those lists are not getting shorter.

Since the launch of its organ transplant program 50 years ago, UC San Diego School of Medicine has been a leader not only in organ transplantation but in developing surgical innovations to address the dire lack of organs available for implantation.

FRESH BREATH

In the 1970s, UC San Diego developed what is today an internationally recognized surgical program to treat a deadly condition in which scarlike tissues clot and clog the lungs, resulting in impaired respiratory function, heart failure and death. Called pulmonary thromboendarterectomy or PTE, the novel surgical procedure is highly specialized but lifesaving.

"Before PTE, critical pulmonary issues were only treated with a heart and lung transplant," said Stuart Jamieson, MB, Distinguished Professor of Surgery. "The surgery grew out of the necessity to find alternative ways to treat patients in the face of organ donor shortages."

The PTE program was established at UC San Diego School of Medicine by Kenneth Moser, MD, pulmonologist, and Nina Starr Braunwald, MD, who was among the first female surgeons to perform open heart surgery.

"They set the groundwork for a truly innovative approach," said Jamieson, who became director of the PTE program in the 1990s. "Pulmonary hypertension from blood clots was not always looked at as a disease. Now, it's recognized as a disease, and because of UC San Diego's pursuits, one that can be cured."

PTE is an open chest surgery, but in its early days was performed through one side of the patient's body, and only on one lung. Today, the patient's body is cooled, and the blood is completely drained. Brain activity is temporarily flatlined. The bypass machine is stopped for 20 minutes, while the surgeon races against the clock to remove blockages from each lung.

UC San Diego Health has performed more than 3,700 PTE procedures, more than any other institution in the world. Patients worldwide are referred for the procedure. It is a global model with the lowest mortality rate.

Michael Madani, MD, chief of cardiovascular surgery, has upped the PTE game. He is using novel techniques from minimally invasive and robotic cardiac surgery.

"It takes an incredible amount of focus to work with such tiny arteries. Every second and every movement counts," said Madani. "We are tirelessly searching for new treatments and techniques to preserve our patient's heart and lungs so that transplantation is not needed."

"We are tirelessly searching for new treatments and techniques to preserve our patient's heart and lungs so that transplantation is not needed."

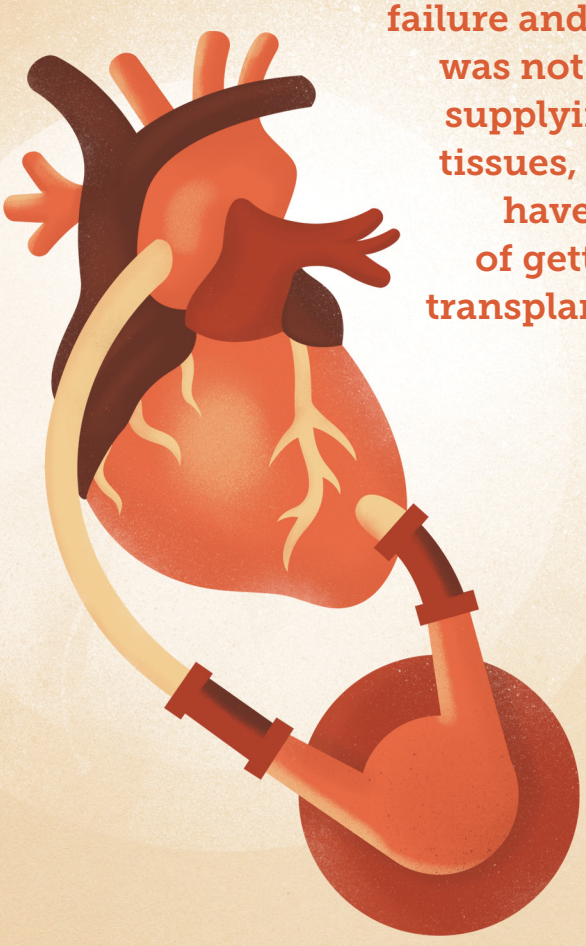
— MICHAEL MADANI, MD

TWO LEFTS MAKE IT RIGHT

The first human heart transplant occurred in 1967, just a year before UC San Diego School of Medicine opened. The patient survived 18 days. In the years since, much has been learned. Heart transplants today are comparatively common and dramatically more successful. More than 2,000 occur in the U.S. annually. UC San Diego Health surgeons perform the procedure dozens of times each year.

But one problem persists: There aren't enough donor organs. Nearly 4,000 persons are on the national heart transplant waiting list; some will die waiting.

Left ventricular assist devices or LVADs are small mechanical pumps implanted inside the left ventricle—one of the heart's four chambers—to help the weakened organ pump blood. LVADs do not replace the heart, but they can mean the difference between life and death.



"In the past, if someone had heart failure and their heart was not adequately supplying blood to tissues, they would have the option of getting a heart transplant or dying."

— ERIC ADLER, MD

"In the past, if someone had heart failure and their heart was not adequately supplying blood to tissues, they would have the option of getting a heart transplant or dying," said Eric Adler, MD, a cardiologist and medical director of heart transplantation and mechanical circulatory support at UC San Diego Health.

LVADs aren't new. The first successful implantation happened a year before the first heart transplant. The technology has improved, but more can be done. There is, for example, no FDA-approved, durable right ventricular assist device.

LVADs aren't designed to function in the right ventricle, but in recent published research, UC San Diego Health surgeons have shown they can work, implanting the devices inside the right ventricles of three patients in dire need of right-sided circulatory support. The pioneering surgeries were successful; all of the patients subsequently received heart transplants.

Since then, Adler and colleagues have performed the procedure 11 times with a 100 percent 1-year survival rate. "There is no standard of care for patients with biventricular failure," said Adler, "so using two LVADs to address this critical need gives patients another treatment option and hope."

In 2011, UC San Diego performed the West Coast's first implant of the world's only FDA-approved total artificial heart. During the four-hour procedure, the patient's diseased heart was completely removed and replaced by a device that rapidly restored blood flow to his entire body. Like LVADs, the device was a "bridge-to-transplant," intended to sustain and improve a patient's life until a donor organ became available.

UC San Diego Health's transplantation programs do not stop at single organs. It's a regional leader in multi-organ surgeries, performing combinations not offered in other hospitals, such as combined heart-lung, heart-kidney, lung-liver-pancreas, liver-pancreas-kidney and heart-lung-liver transplantations. In 2016, UC San Diego surgeons successfully performed the region's first heart-liver transplant. Less than 10 of these surgeries are done in the U.S. each year.

Nearly 4,000 persons are on the national heart transplant waiting list

GROWING GAINS

With chronic organ shortages and temporary devices, the future of transplantation may be do-it-yourself. Researchers across the UC San Diego campus are pursuing this goal, from learning how to grow blood vessels to creating whole organs.

For example, the lab of Tatiana Kisselva, MD, PhD, in collaboration with others, is developing techniques and methods for isolating liver cells ideally suited for use in 3D-bioprinted tissue applications. Other UC San Diego researchers have created miniature sections of functioning liver tissue involving different types of cells and its own blood supply.

Such bioimprinted liver tissue is derived from induced pluripotent stem cells, which are also being explored as a building material for everything from regenerated eye lenses damaged by cataracts to restoring bone lost to disease.

Open small…

Just over a decade ago, UC San Diego Health pioneered the ultimate in minimally invasive surgery, a procedure done without incisions. Instead, surgeons operated through natural body openings, such as the mouth, vagina or anus.

They called it Natural Orifice Translumenal Endoscopic Surgery, or NOTES. The media, taking quick note, called it something else: bizarre.

"UC San Diego was the first health system in the United States to remove an appendix through the mouth," said Santiago Horgan, MD, chief of minimally invasive surgery. "It was a phenomenal experience for the patient, who was able to avoid multiple incisions, and who experienced no pain."

Indeed, the patient's only postoperative complaint, in fact, was a sore throat. Within a week of surgery, he was doing sit-ups, not the typical activity for someone who's just undergone abdominal surgery.

Fast-forward to today: More than 200 patients have undergone NOTES at UC San Diego Health.

"We are always pushing the limits of surgery to benefit patients," said Horgan, who directs the Center for the Future of Surgery at UC San Diego School of Medicine. "With new technologies, we are creating safer surgeries with better patient outcomes, such as less time under anesthesia, less pain and fewer hernias."

NOTES is now offered as a standard of care for many surgical procedures. Hybrid versions have been developed for weight loss surgeries, treatments of swallowing disorders and tumor removal. While some patients remain skeptical, the research results are persuasive.

In a study published in the *Journal of Surgical Endoscopy*, Horgan and his research colleagues noted average pains scores, on a scale of 1 to 10, ranging from zero to 2.5 after a NOTES surgery.

"Typically, we don't recommend pain medication for pain less than four out of 10," said Horgan, the study's first author. "I have seen up to four times less postoperative pain with NOTES compared to traditional open surgery."

"We want to see smaller scars, or better yet, never see them," said Horgan. "Fifty years from now, surgery will be a whole new field. New articulating tools, magnets, and stem cells will all come into play.

THE DOCTRINE OF DOCTORS

By Jacqueline Carr

The art and science of medicine evolves, but the School of Medicine's goal is constant: Create physicians who are as compassionate as they are brilliant.

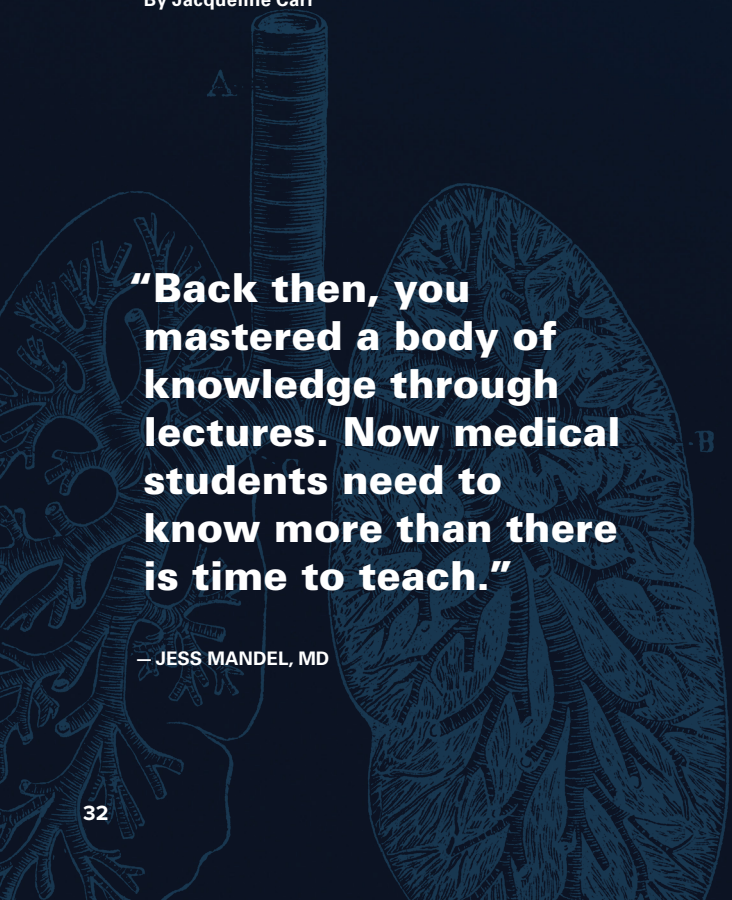
IN A FEW MONTHS, a new class of students will begin studies at UC San Diego School of Medicine, future doctors in pursuit of future careers. They will look a lot like the inaugural class that opened the school 50 years ago.

But this new generation will be working toward much different jobs. They will become trained clinicians, of course, but also stewards of society's resources, medical economists, efficiency experts, disparities reductionists and big data gurus. Some will possess a CEO's business acumen.

They will enter a world as complex as the diseases they treat.

With each scientific discovery, there is more to know every year, said Jess Mandel, MD, former associate dean for undergraduate medical education at UC San Diego School of Medicine. The way medical care is delivered is more complex, requiring more technological interfaces and teamwork. Learning to become a doctor is harder than ever.

"Since 1968, UC San Diego School of Medicine has evolved in innovative ways with its curriculum and training," said Mandel. "Back then, you mastered a body of knowledge through lectures. Now medical students need to know more than there is time to teach. Back then, patients took on faith recommendations for care. Now, patients want to understand their treatment based on their physician's perspective and their own research. These shifts have radically altered medical education."



"Back then, you mastered a body of knowledge through lectures. Now medical students need to know more than there is time to teach."

— JESS MANDEL, MD

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MODERN STETHOSCOPES

Not everything about medical school has changed. Students still attend lectures and still dissect human cadavers. To understand anatomy in three dimensions, the body's structures are best experienced with the eyes and hands. With modern simulation technology, physicians-in-training can now also test procedural skills, including laparoscopy, robotics and endoscopy.

"In medicine today, there is an increasing use of ultrasound beyond radiology," said Mandel. "It is a critical tool used in many standard-of-care procedures. Ultrasound serves the dual role of teaching anatomy, but also as a point-of-care device for placing central lines, draining abscesses and locating blood clots.

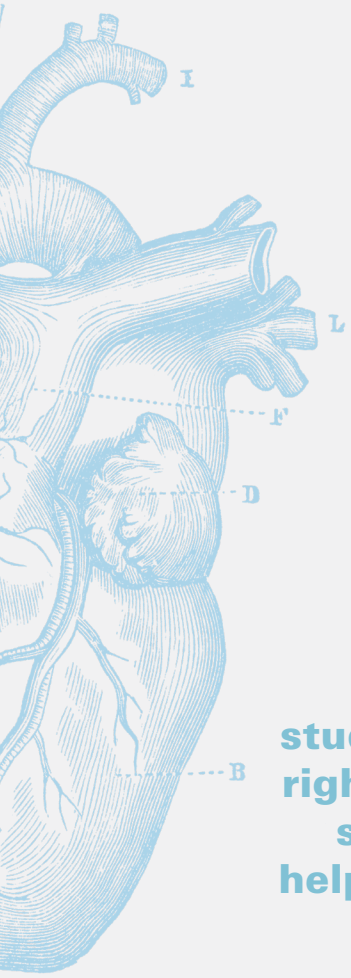
"Our goal has been to introduce ultrasound use to first-year medical students without making it overly disease focused," said Anthony Medak, MD, associate professor. "They learn ultrasound from many houses of medicine, including emergency and internal medicine, cardiology, radiology, critical care and OB-GYN. Ultrasound training is part of the preclinical curriculum in approximately 30 percent of U.S. medical schools.

"We're not trying to make these doctors professional sonographers. We're trying to introduce them to a safe, portable, inexpensive tool that can be used in almost any specialty to answer a variety of clinical questions."

Medak said ultrasound helps students develop a better understanding of anatomy and physiology. The students serve as models, scanning themselves and each other to look at the heart, lungs and musculoskeletal system.

"It's amazing to see the students faces light up when we look at the joints, knees and hands," said Medak. "With ultrasound, the students can see the tendons of the hand move dynamically as the fingers extend and flex. It comes together visually in real time.

"Time and time again, we can see that ultrasound leads to a better patient experience. We orient medical students to understand that ultrasound impacts safety. It can help narrow down a differential diagnosis from a dozen possibilities to perhaps three. As these young doctors become more clinically oriented, the utility of point-of-care ultrasound becomes increasingly clear."



SAFETY FIRST

"My view is we feel compelled to teach students aspects of cell biology that no one ever uses in practice, and then there isn't enough time for safety and systems," said Ian Jenkins, MD, professor of medicine.

Jenkins designs coursework for fourth-year medical students with class titles like America's Cost-Quality Crisis, Quality Improvement 101, How to Kill Your Patient (Our Most Dangerous Medicines) and Teamwork in Health Care. Students who take these courses are headed into internships and need to be aware of potential risks inside fast-paced, high-intensity clinical environments.

"When I went to medical school, we never heard the word 'teamwork,'" Jenkins said. "We were not taught systems or patient safety and were explicitly told that if something bad happened that it was our fault, and to try harder to be a better doctor.

"We teach our medical students that by putting the right policies, protocols and systems in place, you can help more patients than just the ones in front of you."

— IAN JENKINS, MD

"The fact is, most doctors are already doing their best. What we are teaching today is that teamwork, quality control and patient safety make a difference, and that doctors who are aware of and engage in these systems are more successful."

When doctors take care of one patient at a time, they may not think to improve the system of care in which they operate. Jenkins teaches students how to make the physical environment safer. This means understanding software, machines and devices such as electronic medical records and medication ordering systems. To bring the lesson to life, he leads a group project on understanding blood transfusions and blood banks as part of a hospital ecosystem.

"The project helps medical students see what happens when too much blood is ordered and how it impacts the patient's health and hospital finances," said Jenkins. "We work through the standard of care to understand the necessity of transfusion, how to implement a hospital protocol for care and how to measure results."

Jenkins said that he hopes students walk away from the classes seeing that it can be incredibly rewarding to help patients they may never actually meet.

"We teach our medical students that by putting the right policies, protocols and systems in place, you can help more patients than just the ones in front of you."

"The art of medicine is maintaining this social bond, while simultaneously gathering data, processing it, forming a differential diagnosis and offering a plan. My mentors in medicine are all individuals who are capable of tackling all of these tasks at the same time."

— **LUKE BURNS**
Class of 2018

OSLER APPROVES

One aspect of medical education at UC San Diego that remains true to its forefathers is an emphasis on the Oslerian approach to bedside teaching. The modern twist is that the doctor is also a subject of examination, not just the patient.

With both desire and dread, most medical students are hungry for time with attending physicians. UC San Diego has set up a process for third-year medical students to be observed by a group of highly decorated clinicians.

"The master clinicians directly observe students on the pediatrics clerkship during work, physical examination and clinical reasoning rounds," said Christopher R. Cannavino, MD, and director of Pediatric Medical Student Education. "They get direct, constructive and unfiltered feedback to shape their doctoring skills. This one-to-one mentoring makes a huge impact."

The students are not judged or graded. They receive purely informational feedback on things like eye contact, interpersonal skills and working with other medical professionals. The master clinicians silently observe; then they privately share with the students how they can improve their clinical skills.

"How do you deliver news to a patient that is less than great? How can you be forthright and upfront, while also being compassionate?" said Cannavino. "The clinicians give the students the modeling and even word phrases to communicate better. We fill up their doctor's bag, so to speak.

"We all have different blind spots. Therefore, the feedback varies. Some need help synthesizing seemingly disparate symptoms and putting them together to form a diagnosis. It's not just about getting the right answer. It's about getting their deductive thinking right."

Luke Burns, Class of 2018, described the experience: "I'd never encountered anything like this program in any of my rotations, so honestly I didn't know what to expect. It was a genuine privilege to have someone at the senior attending level offer direct feedback. As medical students, we are accustomed to sneaking bits and pieces of feedback from our supervising residents and attendings in between patients. Knowing that my master clinician had been keenly observing me, I was more inclined to take the advice to heart."

Burns said the program taught him to slow down, speak confidently and organize his presentation in a way that was most useful to the rest of the team.

"This is wisdom I have heard dozens of times before in lectures or conversations with attendings," said Burns, "but it took several sessions with my master clinician, bouncing ideas back and forth, and dissecting my presentations for me to truly understand."

Burns learned that the art of medicine is both social science and hard science.

"I have never struggled to communicate with a patient, to be friendly and approachable. The art of medicine is maintaining this social bond, while simultaneously gathering data, processing it, forming a differential diagnosis and offering a plan. My mentors in medicine are all individuals who are capable of tackling all of these tasks at the same time."

WHO'S APPLYING

Carolyn Kelly, MD, associate dean for admissions and student affairs, said the school has become increasingly selective in accepting applicants.

"The matriculation rate has gone up with fewer and fewer students being accepted to fill the class," she said. In 2016, we accepted only 3 percent of the total number of applicants."

"When we asked students why they were choosing UC San Diego, we learned that the school has a reputation for providing a rigorous education in the science of medicine, along with superlative training in the acquisition of clinical skills."

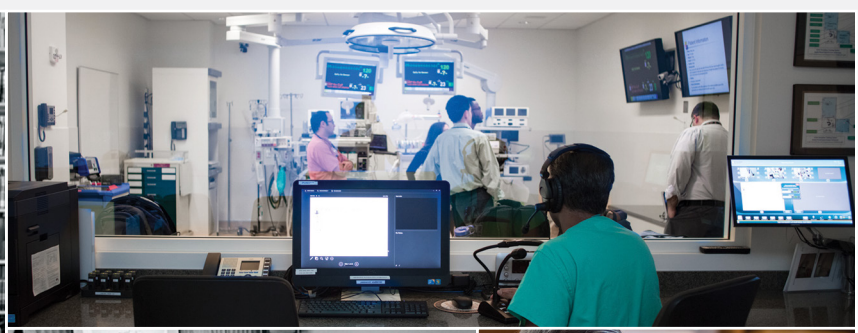
Mandel agreed: "Our ability to compete with elite institutions for top students has improved in the last decade in a tangible way, and we are proud of that. We are in a situation where our students are spectacular, and that becomes one of our greatest recruiting tools. Our students have a credibility with applicants that is higher than that of faculty and administrators."

The type of applicant accepted has changed.

"We are looking for conscientious students who are academically ready to succeed in medical school," said Kelly. "We are seeking students with good interpersonal skills who are ethical and empathic. We look for adaptability and resilience, for students who show promise as future members of a health care team. We hope to uncover their motivation for being part of this profession of service.

"Our students see themselves as members of a larger community facing challenges with health care delivery to all patients. We do our best to help students attain their goals, even if they hit bumps along the way. Academically, we ask a lot of students, and the pace is very challenging. Adapting to this pace can be hard. We try to destigmatize seeking help. Our mantra is that 'asking for help is a sign of strength.' If ever a student feels overwhelmed, there are faculty mentors, advisors and counseling services readily available."

"We are not all supermen and women," said Mandel. "In order to serve others, physicians need to remain healthy. A depressed physician can't be a good or compassionate physician. We have to inculcate patterns of behavior that are sustainable over a doctor's career so that we can be as energetic and compassionate with the last patient as the first."



1968 VERSUS 2018

The inaugural UC San Diego School of Medicine class consists of 47 entering students; 17 percent female.

The 2017 class consists of 134 entering students; 52 percent female.

Just two years earlier, scientists cracked the genetic code — the specific sequence of DNA's nucleic acids that determine the order of amino acids in a protein. This year, they discover restriction enzymes, an important tool for mapping and manipulating genomes.

Hundreds of thousands of whole human genomes have been sequenced, revealing genetic variations associated with disease risk and new drug targets. Advances in high-throughput sequencing, data analysis and gene-editing techniques such as CRISPR-Cas9 drive new diagnostic and therapeutic approaches.

It's not known how many genes, coded in our DNA, make us who we are.

The roughly 19,000 genes in the human genome are just part of the story. UC San Diego researchers are now defining the roles of the epigenome (molecules that control which genes are turned on or off), the glycome (sugar molecules that influence gene and protein function), the microbiome (collections of microbes that live in and on us) and many other factors determining health and disease.

The connection between low-density lipids (LDL, or "bad" cholesterol) and heart disease is hotly debated.

UC San Diego researchers Daniel Steinberg and Joseph Witztum help prove LDL is a major factor, and lowering cholesterol levels is therapeutic. Today, lipid regulators like statins are the most prescribed drugs in the nation.

Fifteen-year-old Robert Rayford, of St. Louis, Mo., is hospitalized with a mysterious viral infection. He would die a year later, the first (retrospectively) diagnosed case of HIV/AIDS in North America. The HIV/AIDS epidemic would officially begin 13 years later.

The HIV/AIDS epidemic hit hard, killing millions globally, but researchers like UC San Diego's Douglas Richman, MD, and sites like the Owen Clinic were in the fight from the beginning. HIV is discovered to be the cause of AIDS. Antiretroviral therapies are developed. Death rates drop; AIDS becomes a chronic but manageable disease.

First validated scales developed for assessing cognitive and functional decline in older adults. It will be another eight years before UC San Diego researchers Robert Katzman and Bob Terry describe Alzheimer's disease (AD) as the most common cause of dementia.

One in 10 Americans age 65 and older has AD. There are now many assessment scales, including "volumetric MRIs" developed at UC San Diego, that measure AD's specific patterns of neurodegeneration. Disease pathology is well understood. There are numerous clinical trials and proposed remedies, but proven therapies still remain elusive.

Nationwide, just one-third of infants born at 28 weeks gestation survive.

More than two-thirds of premature or critically ill infants born at 23 weeks gestation now survive. The smallest baby born at UC San Diego Health is delivered in 2013 at 25 weeks gestation, weighing 11 ounces, or less than a can of soda.

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