endeavor

No 3

A New Vision for Novel Medicines

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WHAT'S INSIDE

SCRIPPS SCIENCE TOUCHES LIVES: VERY PREMATURE BABIES FREQUENTLY DIED OF RESPIRATORY DISTRESS SYNDROME BEFORE THE DISCOVERY OF LUNG SURFACTANT. THE SLIPPERY SUBSTANCE PROTECTS FRAGILE AIR SACS FROM COLLAPSE. TSRI'S CHARLES G. COCHRANE, MD, SPENT TWO DECADES DEVELOPING WHAT IS NOW SURFAXIN (LUCINACTANT), A SYNTHETIC SURFACTANT. TODAY, SURFAXIN IS ROUTINELY GIVEN TO PREMATURE INFANTS TAKING THEIR FIRST BREATHS, SAVING LIVES AND PREVENTING COMPLICATIONS ASSOCIATED WITH ANIMAL-BASED SURFACTANT.

Letter from the President

The Scripps Research Institute (TSRI) has a tradition of outstanding basic research, technology development and the creation of new medicines. Our excellence relies on a world-class faculty, a top-ranked graduate program and, of course, the generosity of our many supporters. In this issue of *Endeavor*, I'd like to share with you my vision for TSRI and how we can support the incredible scientific potential here.

One of the key elements of this vision includes building an endowment to provide institutional support in the form of funding and facilities for our faculty to explore high-risk, high-impact ideas, to increase our understanding of human physiology and impact human disease, and to advance our fundamental knowledge of chemistry and biology. All too often, funding agencies are averse to supporting the bold new ideas and young faculty that transform science. In addition, we need to continue to recruit and retain the world's best faculty, research staff and graduate students.

As part of this latter effort, we are working toward building an endowment to support every graduate student at TSRI. The Skaggs family has long figured in the Institute's success and in this issue, you'll read about Claudia Skaggs Luttrell and her family's recent, transformational gift toward reaching this goal.

At the same time, by bringing together TSRI, the California Institute for Biomedical Research (Calibr) and the Scripps Translational Science Institute (STSI), I believe we can begin to build a new model for nonprofit research institutes—one that not only accelerates the development of innovative medicines for unmet needs, but also provides a self-renewing source of funds to support our research and recruiting efforts.

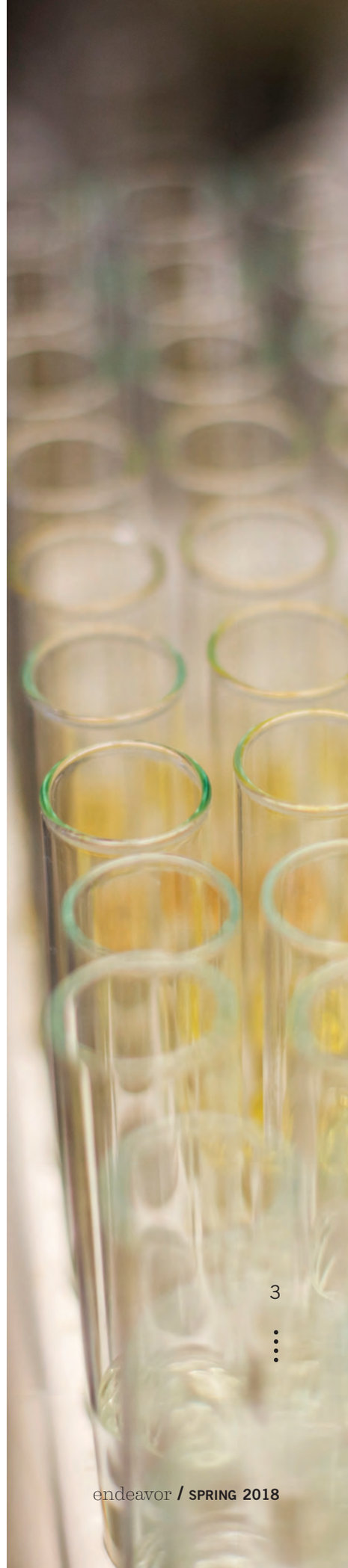
We have a proven track record of creating novel medicines. Two drugs discovered here at TSRI are expected to receive FDA approval in the near future: ozanimod, for multiple sclerosis, and tafamidis, for polyneuropathy and cardiomyopathy. Entering clinical trials in March is a drug by Calibr for osteoarthritis that promotes cartilage regeneration. Calibr plans to enter into additional clinical trials in 2018 and 2019 with two pioneering cancer therapies as well as new treatments for tuberculosis, malaria and childhood diarrhea. And behind these efforts is an entire pipeline of programs created and sustained by the deepening relationship between Calibr and TSRI.

In this issue, you'll learn more about the translational capabilities we are building. You will also see how the recent alignment with STSI is equipping us to utilize clinical research and genomic medicine to further fine tune therapies, ultimately delivering precision medicine. In addition, we're looking to opportunities in regions of emerging scientific excellence and economic initiatives. Leadership from TSRI and Calibr are in discussions with potential international collaborators to implement platforms for accelerating translational research. We'll share more about these exciting efforts in future issues.

We appreciate you and your enthusiasm for our mission. I look forward to a productive partnership as we pursue scientific advancement and the development of new medicines.

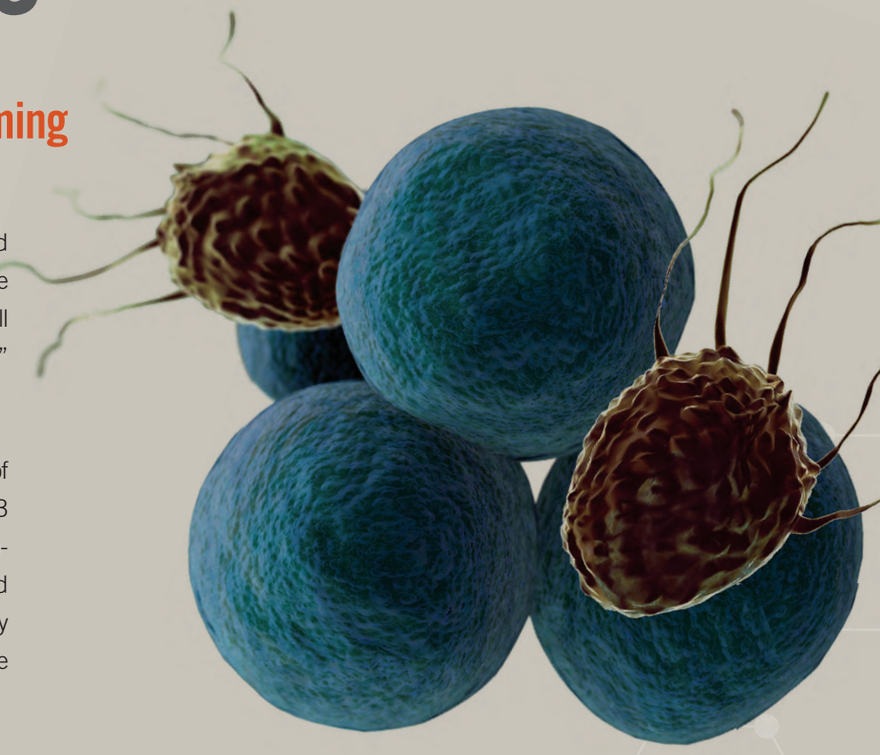
Peter Schultz, PhD

PRESIDENT, THE SCRIPPS RESEARCH INSTITUTE



NEWSHIGHLIGHTS

An important step in programming cancer immunotherapy



When a tumor starts growing, specialized white blood cells called CD8+ T cells rapidly multiply within the spleen and lymph nodes and acquire the ability to kill the tumor cells. But how do these killer T cells "learn" to leave their home base and attack tumors cells?

In a recent study, TSRI researchers from the lab of Matthew Pipkin, PhD, report that a protein called Runx3 programs killer T cells to establish residence in tumors and infection sites. In fact, the researchers found that enhancing Runx3's activity leads to significantly smaller tumors and greater survival rates in mouse models of cancer.

The first promising treatment for the deadly Marburg virus

With a mortality rate of up to 88 percent, Marburg virus can devastate a community in days. Now, TSRI scientists have discovered the workings of the first promising potential Marburg virus treatment: an antibody called MR191. The team, led by Professor Erica Ollmann Saphire, PhD, created a map of the virus' structure and revealed through high-resolution imaging how MR191 targets and neutralizes the virus. This antibody—or a strategy to elicit this antibody in patients—could give doctors a way to successfully treat the disease.

"With this new structure, we can start to see how this treatment works," adds Liam King, a TSRI graduate student and first author of the study.

A plausible recipe for early life on earth

Chemists at TSRI have developed a fascinating theory for how life on Earth may have begun. Their experiments demonstrate that a crude version of the citric acid cycle (used by organisms today) could have been carried out with ingredients likely present on the planet 4 billion years ago. This crude reaction could have kick-started the chemical reactions that led to biological molecules—and life as we know it.

"If you focus on the chemistry, the questions of origins of life become less daunting," says Ramanarayanan Krishnamurthy, PhD, associate professor of Chemistry at TSRI and senior author of the new study.

Osteoarthritis drug enters human trials

More than 30 million Americans suffer from osteoarthritis, a condition that can eventually require joint replacement surgery. A new experimental treatment designed to promote self-healing may one day offer a better alternative. The California Institute for Biomedical Research (Calibr), the nonprofit drug discovery affiliate of The Scripps Research Institute (TSRI), will begin treating osteoarthritis patients this spring with an investigational drug developed as a collaboration between the two institutes. Known as KA34, the drug encourages the adult stem cells that naturally reside in joints to mature into cells that may help heal damaged cartilage.

"KA34 is a flagship program that represents our combined mission at TSRI and Calibr," says Peter Schultz, PhD, president of TSRI and Calibr, "which is to accelerate the creation and delivery of much needed new medicines to patients suffering from disease."

NEWSHIGHLIGHTS

Nobel laureate Kurt Wüthrich leads study of key drug target

Researchers at TSRI have peered deep into the heart of a key protein used in drug design and discovered dynamic structural features that may lead to new ways to target diseases. The protein, called the A_{2A} adenosine receptor (A_{2a}AR), is a member of the G-protein-coupled receptor (GPCR) family, which are the targets of roughly 40 percent of all approved pharmaceuticals.

The more detailed image of A_{2a}AR's signaling mechanism reveals key parts of its inner workings, including an amino acid that acts like a toggle switch to control signaling across the cell membrane.

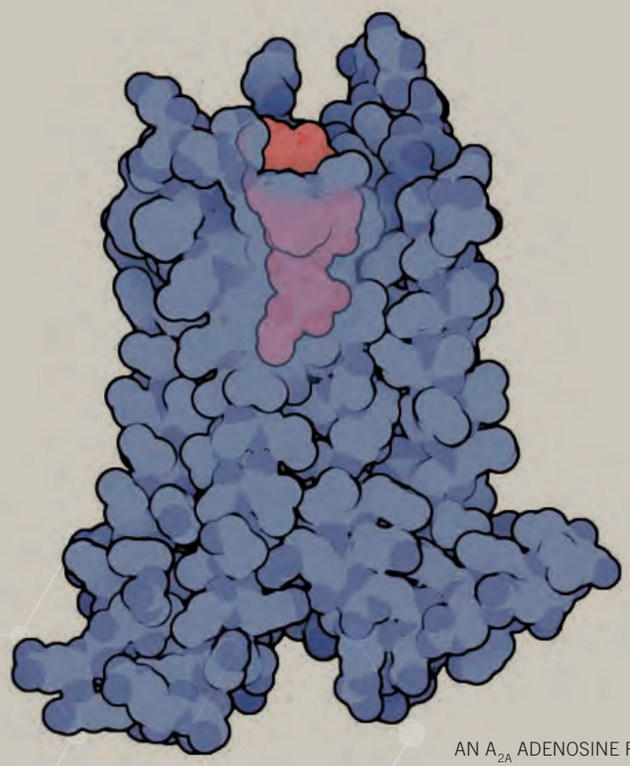
"This basic knowledge is potentially helpful for improving drug design," says Nobel laureate Kurt Wüthrich, PhD, the Cecil H. and Ida M. Green Professor of Structural Biology at TSRI and senior author of the study.

Scientists test new cancer-fighting tactic

Scientists from the Florida campus of TSRI are fighting cancer with what they call "double-decker" antibodies. The new technology ties antibodies and a drug together to produce pharmaceuticals designed to deliver drugs to cancer cells without harming healthy cells and tissues.

"Our new antibody-drug conjugates are built something like a double-decker bus," says TSRI Associate Professor Christoph Rader, PhD. "The upper deck is a targeting antibody that locks onto a cancer cell, while the lower deck is a catalytic antibody that carries the drug."

Already, the double-decker strategy has proven highly effective against HER2-driven breast cancer, multiple myeloma and non-Hodgkin lymphoma in both cell and animal model studies.



AN A_{2A} ADENOSINE RECEPTOR
Illustration courtesy of David Goodsell, PhD

TSRI lab gets first complete look at protein behind sense of touch

TSRI scientists have solved the mystery of the structure of Piezo1, a member of a family of proteins that convert physical stimuli such as touch or blood flow into chemical signals. The findings point the way to targeting diseases where Piezo1 is mutated, such as dehydrated hereditary stomatocytosis and congenital lymphedema.

The researchers used an imaging technique called cryo-electron microscopy to show that Piezo1 is made up of three curved "blades" circling a central pore. The researchers believe these blades move in response to mechanical force, which opens and closes the pore to let ions through to send the signal to communicate touch.

"This structure provides a fundamental understanding of how proteins sense mechanical force, and will shed light on regions within Piezo1 that can be targeted using small molecules or antibodies," says Ardem Patapoutian, PhD, a TSRI professor and Howard Hughes Medical Institute investigator, who co-led the new study with TSRI Professor Andrew Ward, PhD.

Florida spinoff to tackle rare genetic disease

People born with the rare genetic disorder Prader-Willi syndrome suffer from an insatiable appetite they cannot control—which can lead to type 2 diabetes and other life-threatening conditions. At TSRI, scientists including Associate Professor Patricia McDonald, PhD, are leading biochemical research to find a treatment for the disorder.

McDonald's research has led to the new startup Calm Therapeutics. The company will call TSRI's Florida campus its home as it investigates a potential new drug to treat the uncontrollable hunger that comes with Prader-Willi. Calm Therapeutics is supported by the generosity of Josilyn's Faith Foundation for Prader-Willi Syndrome Inc., a New Jersey nonprofit.

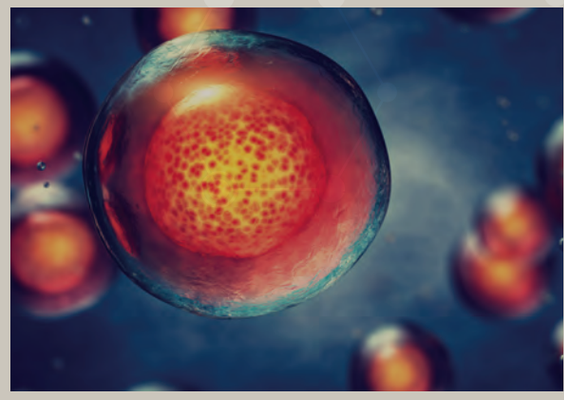
Expansion Therapeutics earns $55.3 million in venture capital

With $55.3 million in new venture capital, TSRI spinoff company Expansion Therapeutics is poised to investigate treatments for muscular dystrophy and as many as 30 other currently untreatable diseases known as "expansion repeat disorders." The company's work is based on technology developed in the lab of TSRI Professor Matthew Disney, PhD.

> "I want very much to see our basic discoveries get to patients."
>
> —MATTHEW DISNEY, PHD

A better understanding of stem cells

A new study led by TSRI Professor Donald Phinney, PhD, sheds light on the protein p53, which appears to be a crucial factor that determines how mesenchymal stem cells grow and differentiate. When the researchers deleted p53, the cells became immortal but quickly developed into bone. A slightly higher level of p53 prompted the cells to differentiate into fat cells, but not bone. These results provide insight into how these cells should be studied for clinical purposes.



AWARDS+GRANTS+HONORS

Researchers receive $10M grant to address alcohol dependence

Professor Barbara Mason, PhD, is leading a new study to determine how long-term alcohol use changes the brain. She and her colleagues have received a $10 million grant from the National Institute on Alcohol Abuse and Alcoholism to support five projects involving molecular pharmacology, neurochemistry, electrophysiology, neurocircuitry and clinical studies.

The team aims to better understand what happens in the brain during the extended withdrawal phase a person goes through when they stop drinking, and to develop ways to treat that phase and prevent relapse. “There hasn’t been a new pharmacological treatment for alcohol dependence in decades,” says Mason. “We want to change that and help facilitate a return to homeostasis in the brains of people with alcohol use disorder.”

Grant enables TSRI team to investigate deadly viruses

With a new $15 million grant, TSRI scientists are gearing up for an in-depth study of survivors of viral outbreaks. The grant from the National Institutes of Health’s National Institute of Allergy and Infectious Diseases will support the efforts of the TSRI-led Center for Viral Systems Biology to fight Ebola and Lassa viruses.

“Our goal is to help eradicate these diseases by building better diagnostics, designing new drugs and informing vaccine design,” says principal investigator Kristian Andersen, PhD, assistant professor at TSRI and Director of Infectious Disease Genomics at the Scripps Translational Science Institute (STSI). Andersen is co-director of the Center for Viral Systems Biology with Tulane University Professor Robert F. Garry, PhD.

While Ebola virus outbreaks are rare, the 2013–2016 epidemic in West Africa infected more than 28,000 people, killing more than 10,000. Lassa virus causes recurring outbreaks in West Africa, killing thousands of people a year.

Immunologists recognize Havran's leadership

TSRI Professor Wendy Havran, PhD, has received the Distinguished Service Award from the Council of The American Association of Immunologists (AAI). The award recognizes Havran’s contributions to AAI programs and the immunology community over the last 20 years. Havran’s lab at TSRI is dedicated to shedding light on interactions between immune cells and tissues of the thymus, skin and intestine.

Spencer award celebrates Patapoutian's contributions to neuroscience

Ardem Patapoutian, PhD, a TSRI professor and a Howard Hughes Medical Institute investigator, has been awarded the W. Alden Spencer Award for his outstanding neuroscience research contributions. The award, from the Department of Neuroscience and the Kavli Institute for Brain Science at the College of Physicians and Surgeons of Columbia University, was presented jointly to Patapoutian and Harvard Medical School Professor David Ginty. Patapoutian, a member of the TSRI Dorris Neuroscience Center, works to uncover the basic mysteries of human sensory biology, such as the proteins underlying sense of touch and pain.

Disney garners Israel Chemical Society award for work in orphan diseases

The Medicinal Chemistry Section of the Israel Chemical Society has bestowed its Award for Excellence in Medicinal Chemistry in Memory of Barry Cohen to Professor Matthew Disney, PhD, of the Florida campus of TSRI. For more than 12 years, Disney has pursued RNA therapeutics, believing they might offer a path to treat diseases that had been deemed untreatable.

"His group has identified patient-specific therapies targeting orphan diseases, especially RNA-mediated neurological disorders with no known cure," such as amyotrophic lateral sclerosis (ALS) and Huntington's disease, says Ehud Keinan, PhD, president of the Israel Chemical Society. "In addition, he devised candidate drugs for common disorders to which there is a poor prognosis, such as drug-resistant cancers."

Martemyanov receives Abel award for pharmacology advances

Kirill Martemyanov, PhD, professor on the Florida campus of TSRI, has received the 2018 John J. Abel Award in Pharmacology from the American Society for Pharmacology and Experimental Therapeutics. The award recognizes Martemyanov's research into how G protein signaling pathways—which are critical targets for many new therapies—are organized and regulated in the retina, heart and brain.

"What I want to emphasize above all is that all this work is built on contributions of many talented scientists working in the lab over the years—so it is really their accomplishments more than mine," says Martemyanov. "It is certainly a motivation to keep going, making new discoveries, learning new biology and just having fun doing this."

Extending her family legacy…while creating one of her own

CLAUDIA SKAGGS LUTTRELL

ABOVE LEFT: BUST OF BENEFACTOR L.S. "SAM" SKAGGS
ABOVE RIGHT: CLAUDIA SKAGGS LUTTRELL AND DAUGHTER, JENNIFER BERNARDONI

"I am deeply indebted to my father who has been an extraordinary role model in my life."

—CLAUDIA SKAGGS LUTTRELL

If there's a gene linked with generosity, it must be intrinsic to the DNA of Claudia Skaggs Luttrell. Since her election to TSRI's Board of Directors in 2002, she has energetically worked to expand and enrich the educational opportunities at the Institute. Most recently, she joined her siblings in making a substantial lead gift from her family's foundations toward TSRI's $100 million campaign to endow its Graduate Program.

Her passion for supporting education comes naturally: Luttrell's father, noted businessman and benefactor L.S. "Sam" Skaggs, identified education and pharmaceutical research as two of his philanthropic priorities. He and his wife, Aline, made numerous, generous gifts to TSRI during their lifetimes, including a $100 million donation in 1996 to create The Skaggs Institute for Chemical Biology. Luttrell later served as its president.

Upon joining the Board, Luttrell proceeded to build on her father's legacy. She helped establish a joint doctoral program with the University of Oxford, the first such academic partnership in the university's centuries-long history, and currently serves as its chair. The Skaggs-Oxford Program is a cooperative five-year course of work combining chemistry or biology research at TSRI with biochemistry classes at Oxford and leading to a joint PhD/DPhil degree. Keary Engle, an assistant professor in the Department of Chemistry at TSRI, is one graduate of The Skaggs-Oxford Program and one who exemplifies the caliber of scientist the dual-campus program produces. Last August, he received the prestigious "Outstanding Investigator Award" from the National Institutes of Health.

"A multigenerational commitment to supporting science is rare," says Peter Schultz, PhD, TSRI president. "Claudia is advancing her father's mission and, through her example, instilling the passion for philanthropy in her own children." In addition to the lead gift from her family's foundations, Luttrell has made a personal donation to the Graduate Program campaign, as have her adult children, Dallas and Jennifer.

Although the program will be renamed the Skaggs Graduate School of Chemical and Biological Sciences, Luttrell, like her father, remains modest. She prefers working "behind the scenes," serving on a number of civic and national boards and overseeing various programs that better the collective future of humanity by educating young students today.

Acknowledging the personal impact of her family legacy in a graduation ceremony speech, Luttrell once said, "I am deeply indebted to my father who has been an extraordinary role model in my life." Now she has become a role model herself, influencing both her philanthropic peers and the next generation.

NINE CRITICAL DRUGS THAT SAVE LIVES

9

There's no greater reward than touching lives. That's what translational medicine means: moving discoveries to the people who need them.

A life devoted to science requires uncommon persistence. For every great discovery, there may be dozens of disappointments, some years in the making. On the following pages, you will read about nine drugs that exist today due to the creativity, inventiveness, persistence and resilience of TSRI scientists. Their discoveries include multiple disease areas, including cancers, hereditary diseases and autoimmune conditions. Their ingenuity has led to new drugs, but more than that, it has produced entirely new categories of drugs.

These scientists persist because the rewards are priceless: Hearing the cry of a premature baby who might have died without a lifesaving new drug; meeting a rheumatoid arthritis patient able to return to work thanks to an advance. There's no greater reward than touching lives. That's what translational medicine means: moving discoveries to the people who need them.

HUMIRA

Inflammation-blocking monoclonal antibody treatment. Used to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa and uveitis.

BENLYSTA

The first new treatment for systemic lupus erythematosus in 50 years. Monoclonal antibody.

CYRAMZA

A monoclonal antibody used with other drugs to fight stomach and non-small cell lung cancer. Chokes off tumors' new blood vessel growth.

ABTHRAX

Monoclonal antibody therapeutic that blocks anthrax toxins.

LEUSTATIN

A chemotherapy drug that prevents cells from synthesizing DNA; used to treat hairy cell leukemia.

SURFAXIN

A synthetic version of the natural substance premature babies need to help their lungs work when taking their first breaths.

FACTOR VIII

A purified version of the blood protein that helps with coagulation; used to treat hemophilia A.

VYNDAQUEL

Stabilizes the misfolded protein behind cardiomyopathy and organ damage in familial amyloid polyneuropathy.

UNITUXIN

A monoclonal antibody used to marshal an immune response against neuroblastoma.

Humira | Benlysta | Cyramza | Abthrax

The antibodies that became drugs

In 1996, Christoph Rader, PhD, hopped a plane from Switzerland to San Diego. He was headed to a postdoctoral position with a lab at The Scripps Research Institute (TSRI) where investigators were trying something bold with antibodies.

Antibodies are our built-in defense against disease. They have evolved to identify and bind with proteins—called antigens—on the surface of germs or other threats. Antibodies kill bacteria, neutralize viruses and destroy tumor cells. But for a long time, most researchers thought antibody molecules were too big—and too expensive to manufacture at a large scale, for therapeutic uses.

Richard Lerner, MD, then president of the Institute, had a different take. Antibodies have a talent for precision-targeting a multitude of threats, and that intrigued him. Too many medicines cause unwanted side effects. Some, like chemotherapies, take out healthy cells with the bad. "That's like setting off a hand grenade in a room full of people," says Lerner.

Custom antibodies might offer a way to avoid such collateral damage, Lerner and colleagues agreed. Lerner and TSRI faculty Carlos Barbas, PhD, and Dennis Burton, PhD, focused on solving a variety of problems that stood in the way of antibody-based therapeutics.

In a matter of years, the scientists had become leaders in an international race to bring antibodies into the clinic. Rader wanted to be a part of that work. In the Barbas lab, he jumped into a cutting-edge field that continues to change medicine and save lives.

"TSRI was one of the hotbeds of this revolution," Rader says. "TSRI was the best place to do this research."

Gearing up to make new medicines

The work built on 1986 research published by the Lerner lab, together with the lab of Peter Schultz, PhD (now TSRI president). That paper showed how to produce antibodies that work as "designer" protein catalysts. The researchers demonstrated that by binding certain small molecules tightly and precisely, antibodies could behave like "designer" enzymes and catalyze necessary chemical reactions.

ANTIBODIES are our built-in smart defense against disease. Antibodies kill bacteria, neutralize viruses and destroy tumor cells.

Binding a catalytic antibody to a small molecule was an important feat, but could antibodies also be programmed to act like drugs and bind to desired disease targets? To find out, researchers needed a way to label antibodies to study their behavior.

Simultaneously with a lab in the United Kingdom, TSRI researchers solved this second big problem in 1989 with the development of a technology called phage display. With this technology, scientists package antibody genes inside an envelope of viral proteins. An antibody protein sticks out of the package, ready to bind with relevant disease targets. Scientists can then read the label on the antibodies like a barcode to see which ones really work against disease—and then produce more of them.

Next came an important step: making new antibodies that the human immune system wouldn't see as invaders. Starting in the 1970s, scientists had used a cloning technique to produce "monoclonal" antibodies in immune cells—"mono" indicating the antibodies were cloned with the ability to precisely target one specific protein. The problem was that the technique was confined to only producing mouse antibodies, which wouldn't work for human patients.

In 1991, the TSRI team reported the first display and selection of human antibodies with the help of phage display. This opened the door for Rader and his colleagues in the Barbas lab to create entire libraries of synthetic, human antibodies.

"They can fly under the radar of a patient's immune system," says Rader.

Their work gave pharmaceutical companies the tools to tackle previously incurable diseases. By the late 1990s, an increasing number of drugs based on monoclonal antibodies were entering clinical trials. "Several of these were based on the technology that was developed at TSRI," says Rader.

Targeting rheumatoid arthritis, cancer, anthrax and lupus

In 2002, the U.S. Food and Drug Administration approved Humira (adalimumab) as the first fully human monoclonal antibody therapeutic. This drug, marketed by Abbott Laboratories, targets a pathway that normally triggers inflammation. Initially approved for rheumatoid arthritis, Humira has now been approved for treating ulcerative colitis, plaque psoriasis, Crohn's disease and several additional forms of arthritis.

By 2003, the group had designed a "hybrid" anti-cancer molecule that combines the power of an anti-cancer drug with an antibody's ability to linger in the bloodstream. The drug stays active—targeting tumor cells—for a week.

With these successes as motivation, Rader, by then a TSRI assistant professor, and his colleagues, kept chipping away at challenges in antibody therapeutics. "I hadn't experienced this interface of chemistry and biology, at this intensity, running through a single lab before. It was tremendously inspiring," says Rader. "Everyone wanted to build new molecules and be creative."

In 2006, an experimental treatment for inhalation anthrax, Abthrax, was purchased by the U.S. government to protect against potential bioterror attack. The treatment, a monoclonal antibody engineered to destroy the anthrax toxin, was also developed using techniques invented at TSRI.

Rader says he could never have predicted the success of antibody-based therapeutics. So far, 30 monoclonal antibody

therapeutics have been approved for cancer therapy alone. The top three cancer drugs currently prescribed are all antibody-based.

"These drugs have given life to people who otherwise would have not survived," says Rader.

Phage display technology developed at TSRI is also credited with leading to the drugs Benlysta (belimumab), approved in 2011 to treat lupus, and Cyramza (ramucirumab), approved in 2014 to treat gastric and non-small cell lung cancer.

Pharmaceutical companies today have even developed antibody therapeutics for pets—starting with therapies for canine lymphoma and dermatitis. "I would have never thought in the 1990s that there would be a market for manufacturing antibodies for dogs," says Rader. "It just shows that antibodies are a tremendously modular and successful platform."

Toward the next generation of therapies

Antibodies have truly become the tools Rader, Lerner and their colleagues dreamed of—and the research continues.

Recent projects include a groundbreaking technology from the Lerner lab that lets scientists artificially produce hundreds of millions of distinct antibodies within large cultures of mammalian cells. The sheer number of antibodies that come from this technology boosts the odds of finding antibodies that can bind with disease targets. Scientists can use these antibodies like markers to discover new biological pathways in the body—pathways that could be targeted with drug molecules.

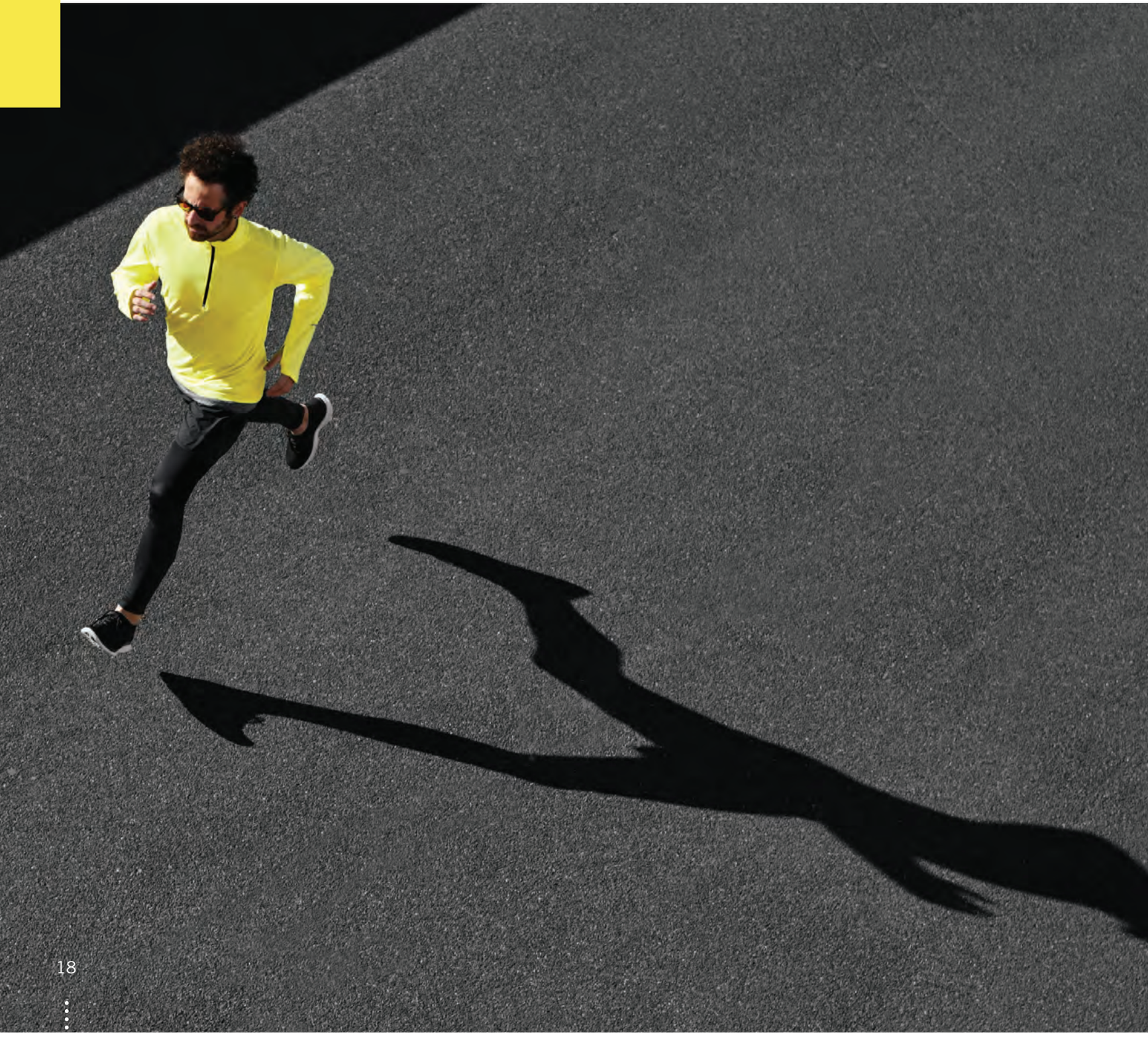
This work has already led to fascinating insights into the immune system's workings. For example, in 2013 Lerner and colleagues used new antibody libraries to identify an antibody that unexpectedly converts bone marrow stem cells into nerve cells.

Together with TSRI scientist Sydney Brenner, PhD, Lerner has also expanded on the principles learned from phage display to build up DNA-encoded chemical libraries, where individual organic molecules are given DNA "barcodes" and tested for their ability to bind with disease targets. In 1992, Brenner and Lerner published the seminal paper on DNA-encoded libraries that has now launched a revolution in small-molecule drug discovery.

More than 2,000 miles away on the Florida campus of TSRI, Rader is carrying antibody research forward. He is proud to help build on the legacy of Barbas, who died of cancer at the age of 49 in 2014. In a poignant epilogue, TSRI researchers are now collaborating with scientists at the University of Pennsylvania to develop an antibody therapeutic for the type of cancer that killed Barbas. The therapy will enter clinical trials later this year.

After working as an investigator with the National Cancer Institute for nearly a decade, Rader returned to TSRI in 2012 to pursue new cancer treatments. He's found ways to target hard-to-treat cancers by using antibodies to deliver toxic drug payloads straight to tumor cells, while avoiding healthy cells. His team recently developed a new class of these "antibody-drug conjugates" that, for the first time, uses a catalytic antibody developed in the Barbas and Lerner labs to attach the drug.

"That's the next generation," Rader says. "And it's exciting to be part of it."



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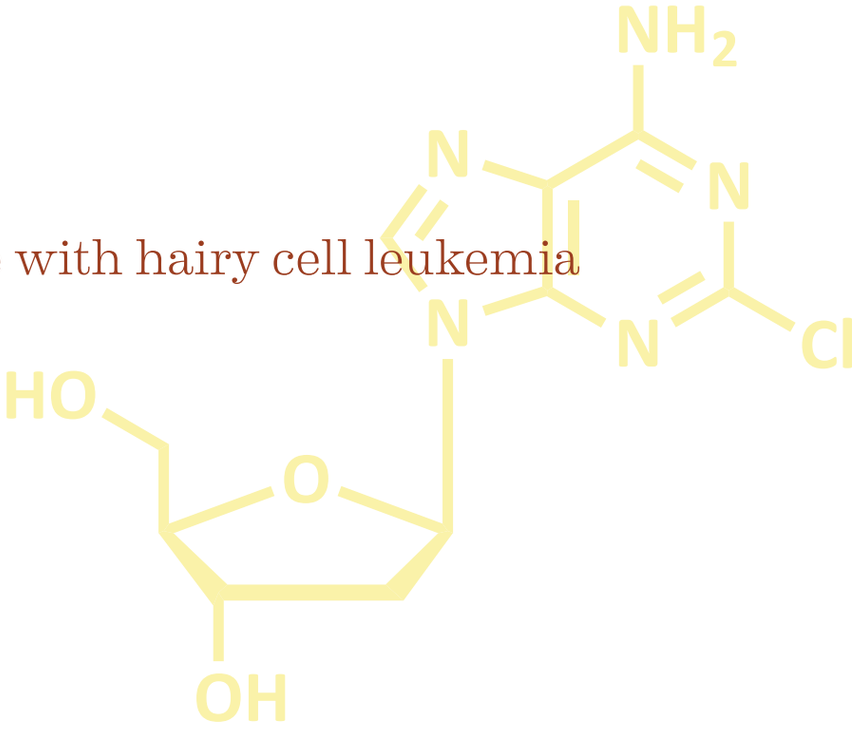
Leustatin

An answer for people with hairy cell leukemia



Remember the gripping movie *The Boy in the Plastic Bubble* about an immunocompromised child who lived in a protective isolation room? Back in the 1970s and early '80s, tragic cases of inherited severe combined immunodeficiency captured public attention. They also inspired a new approach to treating some leukemias. At TSRI, Dennis Carson, MD, noted that many immunodeficiency cases stemmed from a lack of an enzyme necessary for the maturation of T-cells and antibody-producing B-cells, called adenosine deaminase. With colleague Ernest Beutler, MD, he reasoned that blocking the enzyme could be a useful strategy against blood cancers that featured the opposite of the disorder afflicting young David in the movie, overproduction of the immune cells he lacked.

Thus, was born Leustatin, (cladribine) a drug that disrupts adenosine deaminase in B- and T-cells. Because it generally doesn't impact other cells, it doesn't have the side effects that most other cancer drugs have. An estimated 1,000 people a year in the United States will be diagnosed with hairy cell leukemia, so named for the appearance of its B-cells under a microscope. Before the advent of drugs like Leustatin, treatment options were much less encouraging. Patients usually had to have their B-cell-swollen spleens removed, many took harsh chemo drugs, and the 70 to 80 percent survival rate within 5 years of diagnosis left patients in need of better options.

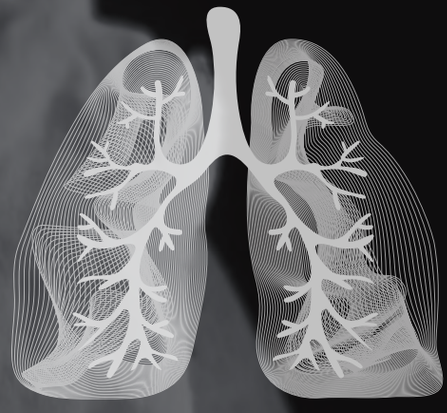
Leustatin was FDA-approved in 1993 and soon became a widely favored first-line therapy for hairy cell leukemia—as it remains today. Patients typically experience remission lasting a decade or longer after a single 5– to 7–day course of treatment.

But there is more to the Leustatin story. The drug's dramatic effectiveness and high tolerability led TSRI's Jack Sipe, MD, a neurologist with expertise in treating multiple sclerosis (MS), to wonder if it might work against that disease, too. In a 1994 clinical trial reported in *The Lancet*, Sipe and colleagues found that Leustatin stabilized or improved disease markers in treated MS patients, whereas those markers worsened for placebo patients.

After a lengthy clinical testing phase, Leustatin won approval from the European Medicines Agency for use against MS in August 2017. Approval from the U.S. Food and Drug Administration for that indication is possible this year.

6 Surfaxin

Helping premature babies take their first breath



Over the beeps and hums of hospital machinery came a frightening noise—the sound of a premature baby gasping for breath. She weighed only 3 pounds. Her father stood next to her, watching her chest heave. She clutched his finger with her small hand.

A generation ago, this baby might not have survived. But thanks to scientists at The Scripps Research Institute (TSRI), she was given a drug called Surfaxin (lucinactant) to help her breathe.

Charles Cochrane, MD, was there that day. He invented Surfaxin, so when he heard that doctors would be giving the drug to a premature baby girl, he rushed to the hospital.

"The baby's breathing was just horrendous," he remembers. "Then they gave her the drug and her breathing suddenly became smooth and rhythmic. Her father turned around and grabbed ahold of me. I was in tears."

Breathing easier

This baby is one of the thousands of premature babies with Respiratory Distress Syndrome who have been saved by Surfaxin. The condition strikes preterm infants whose lungs lack surfactant, a coating of rigid proteins that keeps the spherical air sacs in the lungs from collapsing.

According to the World Health Organization, Respiratory Distress Syndrome is the most common complication and a leading cause of death in preterm infants. Patrick Kennedy, son of President John F. Kennedy and Jacqueline Bouvier Kennedy, died two days after his birth by emergency C-section, five and a half weeks before his due date, from respiratory distress.

Surfaxin's journey from laboratory to clinic started in the late 1980s when a doctor named Allen Merritt, MD, brought Cochrane a sample of human surfactant isolated from amniotic fluid. Merritt, a neonatologist working at that time in the Department of Pediatrics at the University of California, San Diego, was hoping to identify the proteins in the sample.

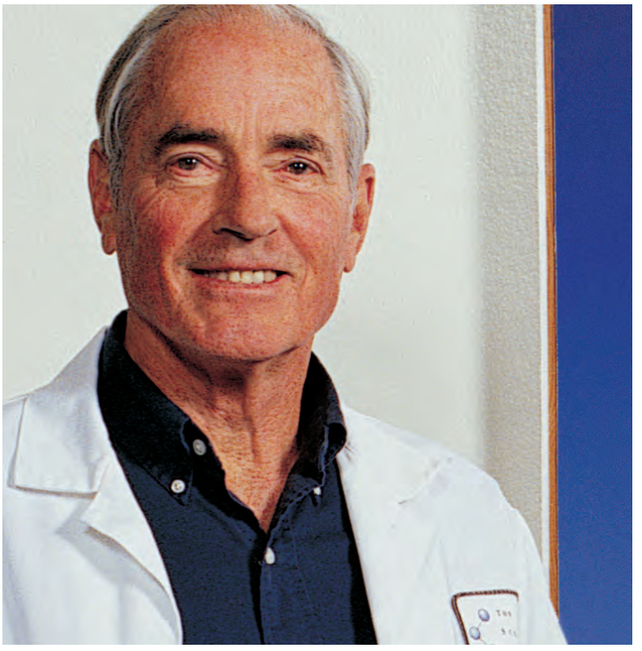
Cochrane had done a lot of work isolating proteins, and his curiosity was piqued. He set up a test using a separatory column, which isolates proteins according to their charges and sizes. That's when things got strange.

Typically, proteins drift down and separate as they interact with the aqueous solution in the column. The proteins in Merritt's sample, however, stayed at the top of the column, forming an opaque, white layer. "These were the first proteins in all of biology not to be aqueous-soluble," says Cochrane. "This was something really crazy."

Though surfactant can consist of several proteins, Cochrane and Merritt believed that surfactant protein B could be the key to keeping the lungs open. They tested it in animal models and saw that breathing improved after they administered the protein.

Merritt, who was new to the research world, remembers being inspired by Cochrane's commitment to learn more.

"It was Charley's genius, really. He said, 'Let's take this protein apart and find out the peptides in it,'" says Merritt.



CHARLES COCHRANE, MD

To picture the structure of surfactant protein B, imagine a backyard fence. Long phospholipids line up in a row, like vertical boards on the fence. But the vertical boards tend to tilt forward and backward. The surfactant protein, or the synthetic peptides that mimic it, are positioned like horizontal crossbeams to interact with the phospholipids and produce lateral stability.

When Cochrane looked at this structure, he spotted a crucial pattern: Though most amino acid residues in the sequence were hydrophobic (repelling water), about every fifth amino acid residue was hydrophilic (attracting water). This combination kept the surfactant in a horizontal pattern and the surfactant dispersed, coating the surface of the tiny air sacs in the lungs.

By focusing on the pattern—not the specific amino acid residues—Cochrane created a simpler version of the protein in his lab.

In a clinical trial of 1,294 infants, published in the journal *Pediatrics* in 2005, Surfaxin showed a significant improvement over a surfactant derived from cattle. A second trial showed Surfaxin to be better than an alternative developed from surfactant from pig lungs.

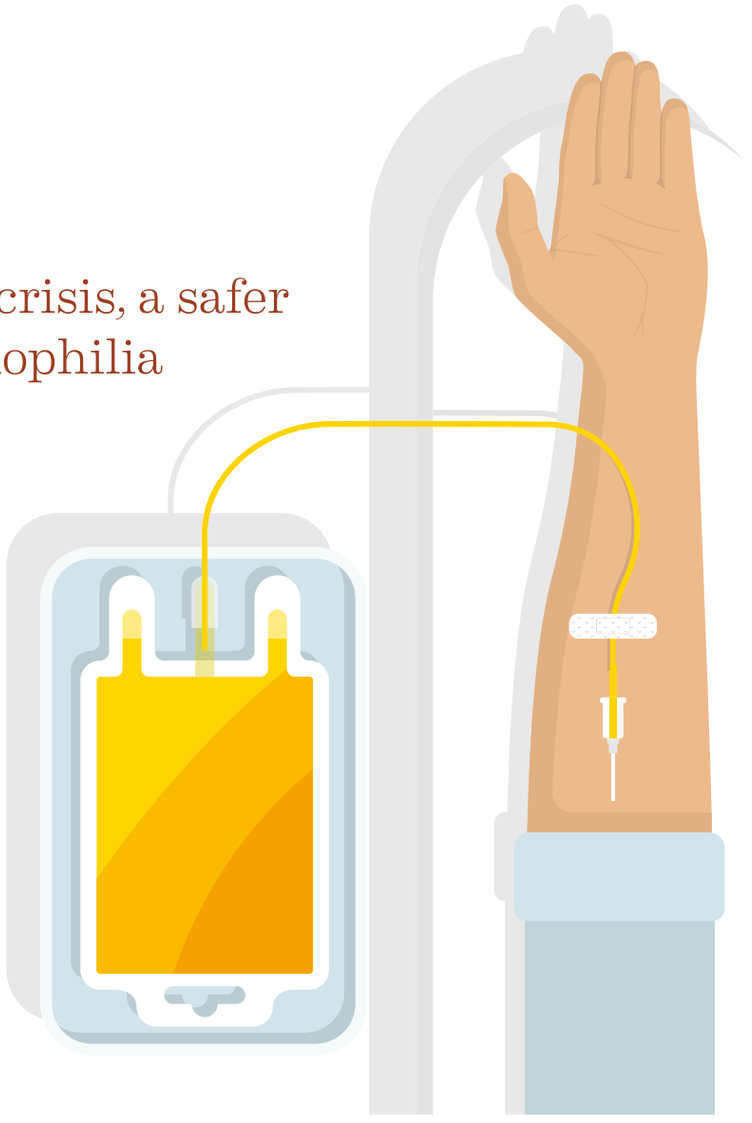
"It worked beautifully," says Cochrane. The drug was approved in 2012.

"It was Charley's open-mindedness, his curiosity and his willingness to analyze the problem that is the reason Surfaxin exists," says Merritt. "It's something that clearly saves lives."

7

Factor VIII

Amid the AIDS crisis, a safer way to treat hemophilia



Patients with a bleeding disorder called hemophilia A lack an important blood-clotting protein, factor VIII. They must rely on transfusions of factor VIII from blood plasma donors to prevent fatal, uncontrolled hemorrhage.

In the early 1980s, people with hemophilia A faced a terrible situation: the transfusions they desperately needed were potentially contaminated with HIV. In the time it took for scientists to identify HIV as the cause of AIDS—and develop a screening test—an estimated 90 percent of people with hemophilia were exposed to contaminated blood.

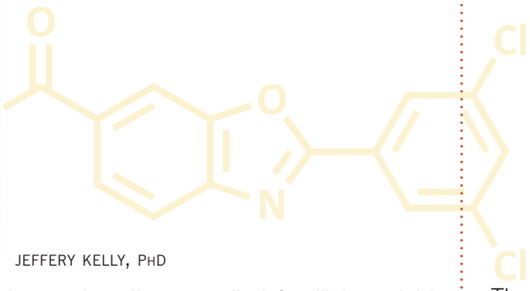
Researchers Carol Fulcher, PhD, and Theodore Zimmerman, PhD, at the Scripps Clinic and Research Foundation (the precursor to TSRI), devised a solution. The team discovered that they could use antibodies like magnets to bind specifically to factor VIII in blood plasma. Viruses and other contaminants could then be washed away, leaving a concentrated, HIV-free dose of factor VIII. This technique led to a product that was 99.9 percent pure, compared with the 1 percent purity of other factor VIII products.

Zimmerman and Fulcher's work led to a drug version of factor VIII, marketed in 1987 as Monoclate, that gave people protection from AIDS-contaminated blood plasma. Today, factor VIII is listed on the World Health Organization's "Model List of Essential Medicines" as a crucial medication needed in any basic health system.

8 Vyndaquel

Slowing the march of familial amyloid polyneuropathy

JEFFERY KELLY, PHD



The gene responsible for a devastating disease called familial amyloid polyneuropathy (FAP) lies on chromosome 18. Called TTR, short for transthyretin, it encodes a protein whose job is to ferry thyroid hormone and vitamin A throughout the body.

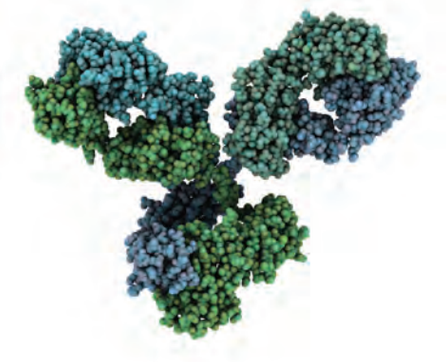
In FAP disease, the garbled gene creates misshapen TTR, which misfolds into toxic junk. This junk collects as amyloid plaque in tissues such as nerves, heart and liver. Nerve cells die. The heart stiffens and organs fail. Left untreated, the disease is typically fatal within 10 years of onset. Liver transplant mediated gene therapy has historically offered sufferers the best hope of survival.

A drug developed in the lab of Jeffery Kelly, PhD, at The Scripps Research Institute (TSRI), Vyndaquel (tafamidis) stops the plaque accumulation by preventing the misfolding. In use in nearly 40 countries globally, it dramatically slows the disease's progression. In the United States, the U.S. Food and Drug Administration recently granted fast-track review status for Vyndaquel.

Notably, the plaque seen in people with FAP resembles what's found in the brains of people with Alzheimer's disease and some other neurodegenerative diseases, says Kelly. The success of Vyndaquel suggests that other amyloid plaque diseases, specifically Alzheimer's, may respond to a similar tactic—stopping the accumulation of toxic misfolded proteins with drugs, he said.

9 Unituxin

A monoclonal antibody fights a childhood cancer



The average high-risk neuroblastoma patient is diagnosed at two years old. Only half of these children beat the disease.

Until recently, doctors were limited to treating this aggressive cancer using chemotherapy, surgery or radiation. But in the 1980s, scientists at The Scripps Research Institute (TSRI) and the University of California, San Diego saw this problem and decided to try a pioneering approach: immunotherapy. The monoclonal antibody they developed, called ch14.18, works by attaching to the surface of neuroblastoma cells. The antibody then directs powerful immune cells to kill the tumor.

Further research at TSRI in animal models gave researchers the "proof of concept" that this therapy could fight tumors in children. Later clinical trials showed that 66 percent of patients who received the therapy had no evidence of cancer two years later, compared with 46 percent of patients who received standard therapy alone.

In 2015, the FDA approved this drug, called Unituxin (dinutuximab), which is the first immunotherapy drug for treating any type of childhood cancer. Like many cancer treatments, Unituxin's serious side effects have limited its widespread use, but its discovery propelled the field of cancer immunotherapy forward.

Tomorrow's TREATMENTS

Envisioning better options for pain relief, multiple sclerosis, ALS and more

The Scripps Research Institute (TSRI) now has more drug candidates in development than at any time in its history, many for rare diseases that have otherwise been neglected by the medical community, including amyotrophic lateral sclerosis (ALS) and Prader-Willi syndrome. That's no accident. Sustained focus on inventing new research methods and boosting the efficiency of experimentation through adoption of industrial methods—including robotics and high-throughput drug discovery—has transformed TSRI into an engine of innovation that is unique in the world.

Together with the Scripps Translational Science Institute (STSI) and our affiliated partner, the California Institute for Biomedical Research (Calibr), TSRI is building translational capabilities that will further accelerate the path from idea to discovery to clinic.

The advanced technologies and biochemistry tools available at TSRI draw some of the most innovative and entrepreneurial scientists in the world. There's nothing more exciting for scientists than to see something they've worked on for years reach the people who need hope and help. Read on to learn about four potential new drugs and one paradigm-changing drug discovery technology that hold great promise for the future.

Prescription for Life

What does it take to turn an idea into a drug?

Opioids, pain-relieving drugs that include Oxycontin and fentanyl, are widely prescribed to relieve the suffering of millions. These same drugs can also cause much suffering.

Patients with chronic pain must increase their dosage as tolerance develops. Because opioids also suppress breathing, higher doses are a key factor in the epidemic of opioid-related fatalities engulfing the country.

Laura Bohn, PhD, a professor at TRSI-Florida, and her colleagues wondered if the paired pain-relieving and suppressed breathing effects could be separated. Marshalling their scientific curiosity and technological expertise, they set out to create a safer opioid. In the later stages of their investigation, Bohn is working closely with scientists at the California Institute for Biomedical Research (Calibr), an affiliate of TSRI focused on translating basic research into new medicines.

Here's their journey.

"Our research is revealing new ways to target the mu opioid receptor to preserve pain relief while avoiding respiratory suppression."

—Laura Bohn, PhD

Focus

Opioids bind to receptors on cells. Bohn has studied opioid receptors, a type of G-protein-coupled receptor (GPCR), for 18 years. She focuses on the mu opioid receptor (MOR), eyeing two proteins: the G-protein pathway, which provides pain relief, and the beta-arrestin pathway, which suppresses respiration.

STEP

1

Robert Lefkowitz won the 2012 Nobel Prize in Chemistry for his work investigating GPCRs.

411: G-protein-coupled receptors (GCPRs) on the cell membrane relay messages that regulate bodily functions. **GPCRs are essential to 30-50% of all modern medicines**.

Target

When Bohn studied mice bred to have no beta-arrestin, she discovered they received pain relief from opioids without experiencing respiratory suppression. The two signaling pathways could work independently. She had her target. Now, could she develop a drug that blocked or muted the beta-arrestin signal while preserving the G-protein signal?

STEP

2

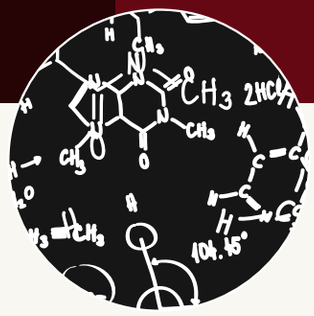
411: Mice and rats comprise **95%** of all lab animals.

Identify

Bohn and TSRI chemist Tom Bannister, PhD, developed over 500 molecules with the potential to activate MOR, while preserving G-protein signaling and dampening beta-arrestin signaling. After six years of study, 60 candidates were identified.

STEP

3



411: Scientists often must screen **thousands of molecules** on compound plates to identify a pool of drug candidates.

Refine

The 60 candidates were scrutinized for biosignaling and refined for safety, stability and sterility, as well as for the ability to enter the brain. Six "representative compounds" emerged. Calibr assisted with further testing.

STEP

4

"We hope to inspire new approaches in treating pain, addiction and mood disorders."

—Laura Bohn, PhD

411: Biosignaling is any signal within a living being that can be monitored and measured.

Test (Lab)

When tested in mice, Bohn's six compounds provided pain relief (some even better than morphine) without suppressing respiration. She published her method for making safer opioids in *Cell* last November, saying, "We've filed for a patent to protect the intellectual property but by publishing, we are giving the tools to the world."

STEP 5

411: Pharmacodynamics: the study of how a drug affects an organism. **Pharmacokinetics:** the study of how an organism affects a drug.

Test (People)

Early in 2019, Bohn expects to submit an Investigational New Drug (IND) application with the FDA. With the agency's approval, a series of clinical trials will take place over several years.

STEP 6

Bohn's work received support from the National Institute on Drug Abuse (NIDA).

411: Only 1 in 1,000 potential drugs graduates to human clinical trials. There, 9 out of 10 fail.

Approve

If the trials succeed, Bohn will send a New Drug Application (NDA), with all of the preclinical and clinical data, to the FDA. The agency has 6-10 months to review and approve.

Meanwhile, Bohn continues her research into the neurological mechanisms underlying pain. "It's important to note that we haven't solved addiction," she cautions. Evaluating the addictive properties of her lead compounds will be part of upcoming studies.

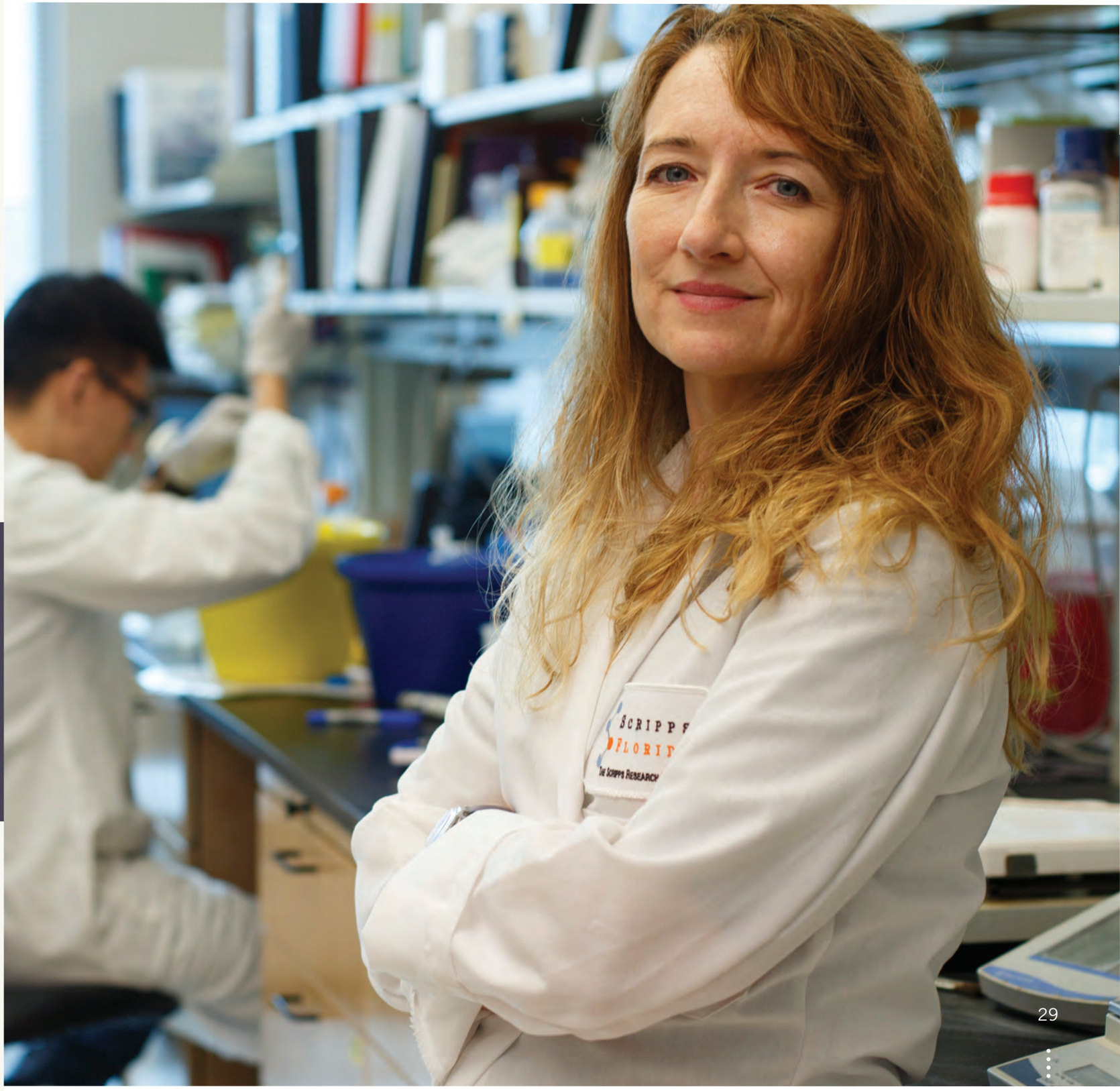
Now that she and other TSRI scientists can optimize the capabilities and translational expertise at Calibr, they'll more quickly turn bold ideas into life-saving drugs.

STEP 7

"Discovering a new drug is every translational scientist's quest and toughest challenge."

—Arnab Chatterjee, PhD
Vice president of Medicinal Chemistry at Calibr

411: The entire cost to research, develop, test and market a new drug exceeds **$1 billion**.


SCRIPPS
FLORIDA
THE SCRIPPS RESEARCH

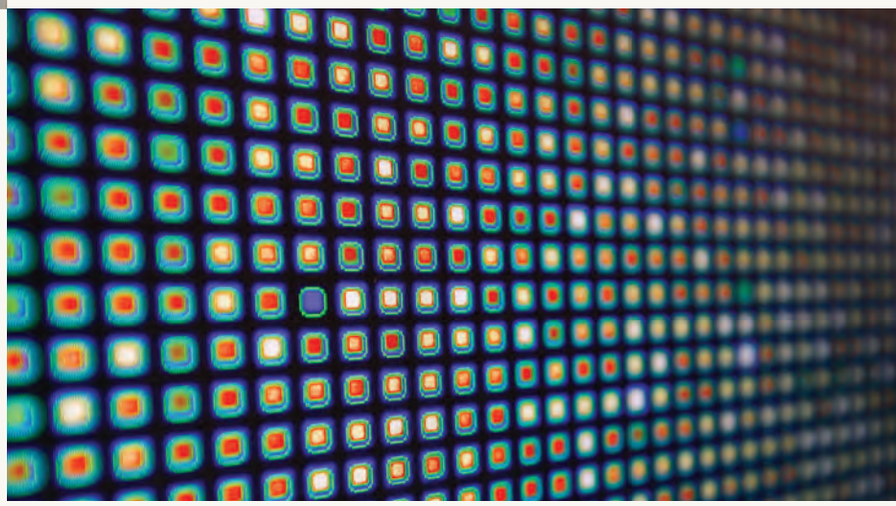
MULTIPLE SCLEROSIS

Innovative treatment protects the brain

CLINICAL TRIALS SUGGEST OZANIMOD COULD WORK BETTER THAN OTHER MS DRUGS AND MARKEDLY IMPROVE QUALITY OF LIFE.

"The ozanimod story highlights the uniqueness of TSRI. There are hardly any other academic institutions in the world that have the multi-disciplinary expertise to discover a new disease-modifying compound and develop it most of the way toward clinical use."

—HUGH ROSEN, MD, PHD



HIGH-THROUGHPUT ROBOTICS "HITS" IDENTIFY PROMISING COMPOUNDS.

Ozanimod is among the most promising molecules ever to graduate from TSRI's translational research. Pending FDA approval, it is poised to become the drug of choice for treating the most common form of multiple sclerosis (MS), and a possible breakthrough therapy for other autoimmune conditions, too.

More than 2 million people around the world suffer from MS, which is caused by inappropriate immune system activity in the brain and spinal cord, and results in damage to nerve fibers. People with MS can experience a wide range of symptoms, from vision problems and difficulties balancing, to anxiety and memory loss. Most patients start out with the relapsing-remitting form of the disease, in which bouts of inflammation and symptoms occur at intervals, and permanent neurological problems accumulate slowly. More than a dozen drugs exist to treat relapsing-remitting MS. But, as for most other autoimmune diseases, no existing treatment really stops the progression of damage, and many have serious side effects.

Ozanimod won't be a cure for MS, but recent clinical trial results suggest it could work better than any other MS drug, and thus markedly improve patient quality of life. "Ozanimod substantially blunts the disease process," says TSRI scientist Hugh Rosen, MD, PhD. "It protects patients not only from new or expanding brain lesions, but also from the loss of brain volume that otherwise occurs over time in relapsing-remitting MS. It thus potentially enables MS patients to avoid the long-term disabilities that change their lives and the lives of those who care for them."

Ozanimod works by hitting cellular receptors called S1P receptors, which help regulate the immune system among other functions. Rosen and his team, in a landmark study published in *Science* in 2002, showed that hitting these S1P receptors in a certain way can have a subtle and potentially useful immune-damping effect: It prevents T cells, heavy weapons of the immune system, from surging out of the thyroid and lymph glands and circulating in the body in response to threats. "The potential therapeutic applications in autoimmune disease were obvious," Rosen says.

HIGH-THROUGHPUT ROBOTICS ENABLED THE ROSEN LAB TO SHORTEN THE OZANIMOD DISCOVERY TIMELINE.

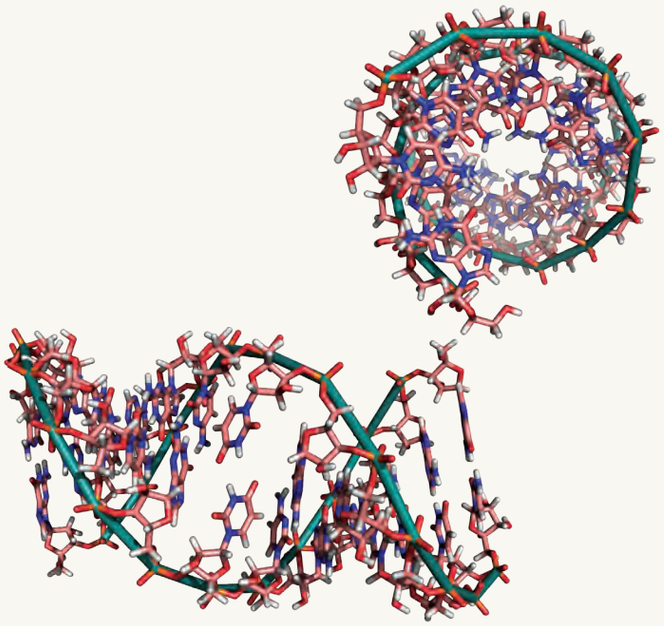
He and his TSRI colleagues, including Edward Roberts, PhD, Miguel Guerrero, PhD and Steven Brown, PhD, soon developed ozanimod—which hits S1P receptors in a way that makes it effective as a T-cell immobilizer while minimizing side effects. Pharmaceutical giant Celgene acquired the rights in 2015 and is now pursuing FDA approval to market the drug for relapsing-remitting MS.

But MS may be just the beginning for this drug. Rosen and Roberts have been working with TSRI scientist Michael Oldstone, MD, and his lab to discover all the biological pathways affected by ozanimod—and the findings suggest a host of other autoimmune diseases that the drug might treat. Celgene is now running clinical trials in patients with ulcerative colitis and Crohn's, the two most common forms of inflammatory bowel disease; results so far have been promising. Other envisioned disease indications include psoriasis, lupus, and Sjogren's syndrome.

"The ozanimod story highlights the uniqueness of TSRI," Rosen says. "There are hardly any other academic institutions in the world that have the multi-disciplinary expertise to discover a new disease-modifying compound and develop it most of the way toward clinical use."

ALS, FRONTOTEMPORAL DEMENTIA, CANCER, MYOTONIC DYSTROPHY TYPE I AND MORE:

Targeting RNA diseases



Matt Disney isn't just inventing medicines—he's opening a whole new front in the war on disease. The drugs he's developing on the Florida campus of The Scripps Research Institute (TSRI) are of the ordinary kind that can be taken as pills. But in a twist, they work by targeting RNAs instead of proteins.

Virtually all existing drugs work against proteins. Proteins are prime targets for drugs because they are crucial for cellular operations. They also tend to be relatively big molecules with complex, stable structures to which drug compounds can fasten tightly and selectively.

RNAs represent a very different sort of target. They are the molecules that cells make when copying out the genetic information contained in DNA. Some RNAs carry genetic instructions for making proteins. Many fulfill other important functions in cells. In principle, targeting RNAs would allow one to influence virtually any process in cells, and thereby treat any disease. The problem has been that RNAs tend not to form the complex, stable structures that proteins form. That makes them harder to hit selectively with ordinary drug molecules.

However, Disney and his lab in recent years have developed a way to decode a subset of RNAs that do possess enough structure to be targeted with normal drugs.

"Our targets are targets that the big pharma companies would never consider because they see them as too risky," Disney says. "But we've been able to de-risk them. Because of these efforts, every big pharma company is starting to pursue RNA as a small-molecule drug target."

Targeting RNA may sometimes be the best option in fighting an illness. That is particularly so when RNA molecules themselves are the immediate causes of illness, as in the so-called repeat-expansion diseases. In this class of genetic ailments, mutations elongate genes, resulting in the production of abnormal, extra-long strands of RNA. These extra-long RNAs can form abnormal loops and other complex structures that often are toxic to the cells they inhabit. Repeat-expansion diseases, which affect millions of people worldwide, tend to be progressive and fatal. "Not one of them has a cure," Disney says.

That may soon change. The abnormal structural complexities of repeat-expansion RNAs in principle make them more targetable with drugs, and Disney is pursuing that opportunity. His years of basic, grant-funded science in this field led to the recent spinoff of a startup biotech company, Expansion Therapeutics, which is now well along in developing candidate anti-RNA compounds to treat this class of ailments. Their most advanced project involves a candidate drug against myotonic dystrophy type 1 (MD1), an inherited disease that kills motor neurons and causes muscle weakness, wasting, and abnormal tensing, in addition to cataracts and heart problems.

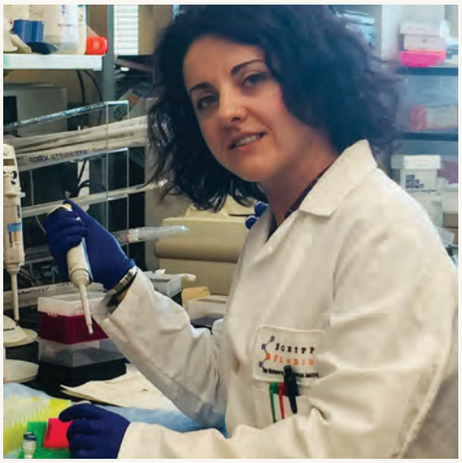
"We've shown that we can hit the RNA target in MD1, and we're now optimizing some promising compounds to maximize their effectiveness and minimize side-effects—everything is looking good so far," Disney says.

He and his team are, moreover, investigating potential drug compounds to help people who have ALS or frontotemporal dementia—many cases of which involve toxic repeat-expansion RNAs. Candidate anti-RNA treatments for Huntington's disease, autism, myotonic dystrophy type 2, and even some infectious diseases and advanced cancers are also in the works.

"The technological platform we've established for finding candidate anti-RNA drugs is applicable to nearly every human disease," Disney says.

PRADER-WILLI SYNDROME

A hunger for a cure



TOP: PATRICIA MCDONALD, PHD
BOTTOM: CRISTINA GRANDE, PHD

Children born with a genetic disorder called Prader-Willi syndrome (PWS) live with a complex set of struggles. Their brains and bodies don't develop normally due to an abnormality of chromosome 15. It typically leaves them with short stature, infertility, intellectual disability and compulsive and autistic behaviors. Most strikingly, PWS kids between the ages of 2 and 8 begin to experience a hunger for food that never goes away for long, and is often so intense that it feels like starvation. PWS kids thus tend to become obese, and eventually develop related ailments such as diabetes and cardiovascular disease.

The hunger in PWS is linked to high levels of the appetite hormone ghrelin. In principle, blocking ghrelin signaling in appetite-related neurons would normalize the desire for food and reverse at least that part of the disease. But the pharmaceutical industry—seeking a blockbuster obesity drug—has been there and done that: compounds designed to reduce signaling through the ghrelin receptor just haven't suppressed appetite significantly in animal tests.

The good news is that scientists at TSRI are now reasonably certain why those prior efforts went wrong. Metabolic disease expert Roy Smith, PhD, showed in studies over the past several years that ghrelin receptor signaling isn't as simple as it looks. On appetite-regulating neurons, the receptor normally combines with another receptor, the dopamine D2 receptor, forming a complex. Working with TSRI chemist Ted Kamenecka, PhD, Smith's lab identified a compound that effectively hits that combined receptor—in a way that successfully suppresses feeding behavior in PWS mice. The compound even reverses abnormal compulsive mouse behaviors that are also seen in PWS patients.

Smith retired in late 2016, but work on the promising compound continues, with support from the Josilyn's Faith Foundation for Prader-Willi Syndrome Inc. and affected families. Kamenecka and his lab are generating new variants of the compound, and receptor expert Patricia McDonald, PhD, and her postdoctoral researcher Cristina Grande, PhD, a Smith lab alumna, are testing them in cell cultures and in mice.

"We're at the stage where we're optimizing the compound's properties as a potential drug to get it ready for testing in people," says McDonald. "We're hoping that ultimately it will help not only people who have PWS but also a much wider group of patients with diabetes, obesity and related metabolic disorders."

HEROIN ADDICTION

Vaccine that blocks highs supports recovery

Most people think of vaccines as giving protection from dangerous viruses or germs—nasty things like measles, meningitis or polio. Chemist Kim Janda, PhD, with the California-based Skaggs Institute for Chemical Biology at The Scripps Research Institute, sees other possibilities. Janda has devised an innovative method that relies upon chemistry to craft vaccines against heroin and other problem street drugs that the immune system wouldn't normally view as an invader.

"Simply stated, our vaccine approach takes advantage of our natural defense system," Janda said. "Our hope is that it will be used to help people who have a substance use disorder and have tried other therapies that have failed."

Using a three-step process, Janda's laboratory assembled vaccines against synthetic opioids such as fentanyl, and stimulants like cocaine, methamphetamine and Captagon—a psychoactive drug reportedly used by ISIS to turn its fighters into "unforgiving killing machines."

Janda's anti-drug vaccines are made by first chemically assembling a hapten, which mirrors the drug's molecular structure. It is then attached to a protein for immune system recognition. The third factor, a chemical adjuvant, or immune response booster, combines with the hapten-conjugate complex to create a vaccine-cocktail, enabling the immune system to spot the drug as a foreign invader and thus build an antibody defense mechanism against it.

Training people's immune systems to seek out and remove a problem drug means the drug is prohibited from reaching pleasure centers in the brain, Janda said.

"With heroin, we developed a dynamic vaccine that blocks not only heroin but heroin's dangerous psychoactive metabolites," Janda said. "Our data suggest the vaccine not only helps with heroin cessation therapy, but also with lethality from the drug, a tragically common occurrence in cases of relapse."

Janda started working on his anti-heroin vaccine long before the current opioid epidemic began to rage in the United States, he said. Back then, he thought it would prove most useful in countries that lacked a proper drug rehabilitation infrastructure. Sadly, the United States' heroin addiction problem has grown so large so quickly that it is overwhelming health systems here. Janda is eager to move the anti-heroin vaccine into human clinical trials.

The incidence of overdose deaths has quadrupled since 1999, Janda said. More than 90 Americans die each day from opioid overdose.

"I know the costs when a family has a member with a substance-use disorder," he said. "Current therapies, while useful, are not solving the problem. We need to come up with new approaches, and a vaccine may just be a new means to help end the addiction cycle."

Visionary architect behind Scripps Florida's neuroscience program

RON DAVIS

The quest to understand learning and memory has intrigued many biologists. For neuroscientist Ron Davis, PhD, it is not only memory that fascinates, but also forgetting; specifically, the removal of already stored memories.

On the Florida campus of The Scripps Research Institute (TSRI), the Davis lab studies the fundamental biochemistry underlying memory and forgetting, revealing that forgetting is not merely a passive process of memory erosion, but also an active one of erasure, apparently necessary for healthy brain function.

Davis first visited the newly created Florida branch of TSRI in 2009, when scientists and staff still worked out of temporary quarters. He thought the opportunity to launch a neuroscience department there was "an intriguing idea," but he had a well-established career at the Baylor College of Medicine, where he worked in model organisms, including the fruit fly, *Drosophila*, to understand the acquisition, consolidation, stabilization and retrieval of memory.

Ultimately, TSRI's exceptional drug-discovery resources and the opportunity to build a new research program in Florida proved enticing. He accepted the position, bringing four of his lab members with him. Over the years, Davis has recruited some of the best minds in neuroscience to staff the department. TSRI Executive Vice President Jamie Williamson, PhD, called the effort "a remarkable job of hitting the ground running," adding that "Ron built up a world-class neuroscience department from scratch."

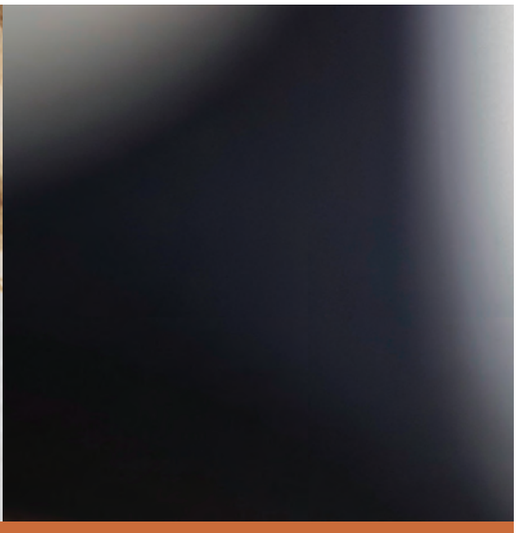
Even as he recruited faculty and managed the department, Davis continued to run his own lab, uncovering important information about the signaling proteins linked with memory acquisition and erasure. His group discovered that the presence of calcium in mitochondria, the powerhouses of all cells, impacts brain development and adult cognition. And he and his team linked bipolar disorder to an unexpected area of the brain called the striatum. The world-class drug discovery infrastructure at Scripps Florida enabled him to assemble a large group of scientists who work on developing therapeutics for Alzheimer's and Parkinson's diseases. Davis' work attracted significant funding, including a recent award of $5 million from the National Institute of Neurological Disorders and Stroke.

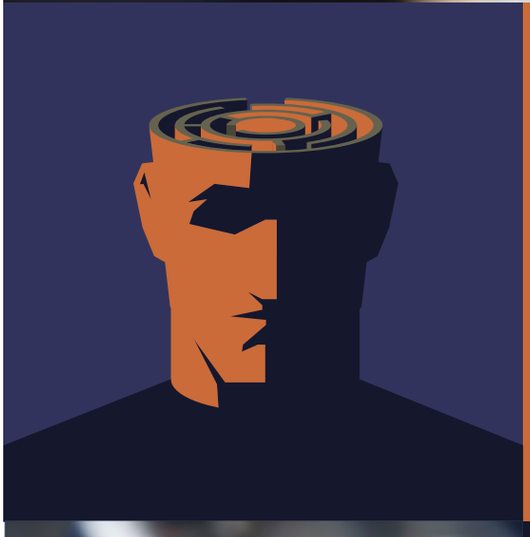
Eight years later, the Florida arm of TSRI's bicoastal Neuroscience Department has grown to nearly 110 people and published close to 200 scientific research papers in top neuroscience journals. In 2016, Scripps Florida Neuroscience faculty members and their labs attracted nearly $12 million from the National Institutes of Health.

Earlier this year, as part of an Institute-wide chair rotation, Davis turned over his role to colleague Kirill Martemyanov, PhD, an expert in the neural signaling pathways that control many fundamental processes, including excitability, sensory perception and synaptic transmission. Martemyanov says he has long admired Davis' leadership. "Throughout the years, I have really appreciated his dedication to creating a highly collaborative, collegial and comfortable environment, assembling top-notch infrastructure and ensuring smooth operations of pretty much everything."

The brain presents a complex frontier, much of it still uncharted. Many questions remain to be solved, says Davis. "We need to figure out what is downstream—walk down the pathway to find the complete signaling system for forgetting. We are very early in this research. In addition, we urgently need to find new therapeutics to treat disorders of the brain."

FACULTY PROFILE





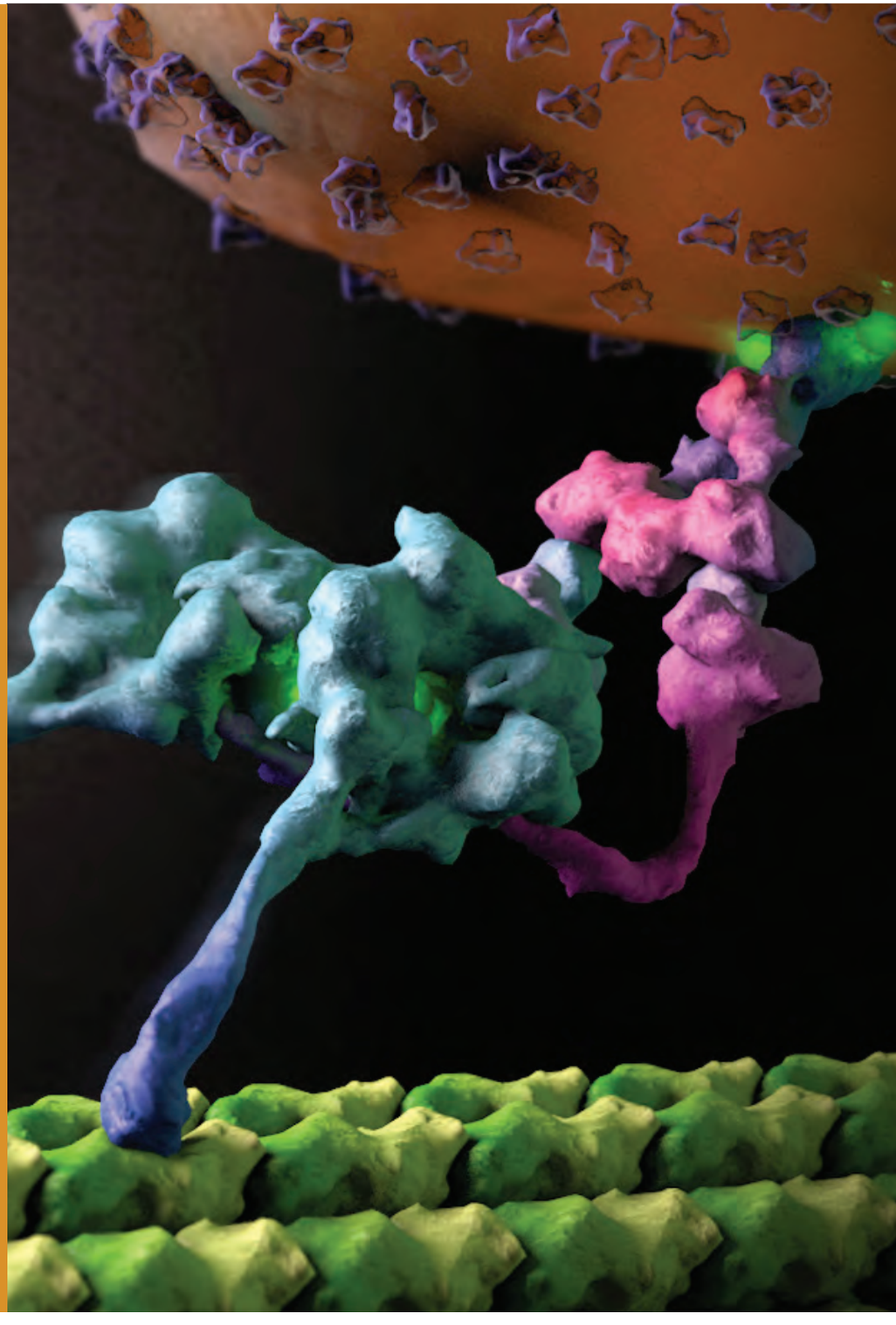
The quest to understand learning and memory has intrigued many biologists. For neuroscientist Ron Davis, PhD, it is not only memory that fascinates, but also forgetting; specifically, the removal of already stored memories.

SEEING INTO LIFE

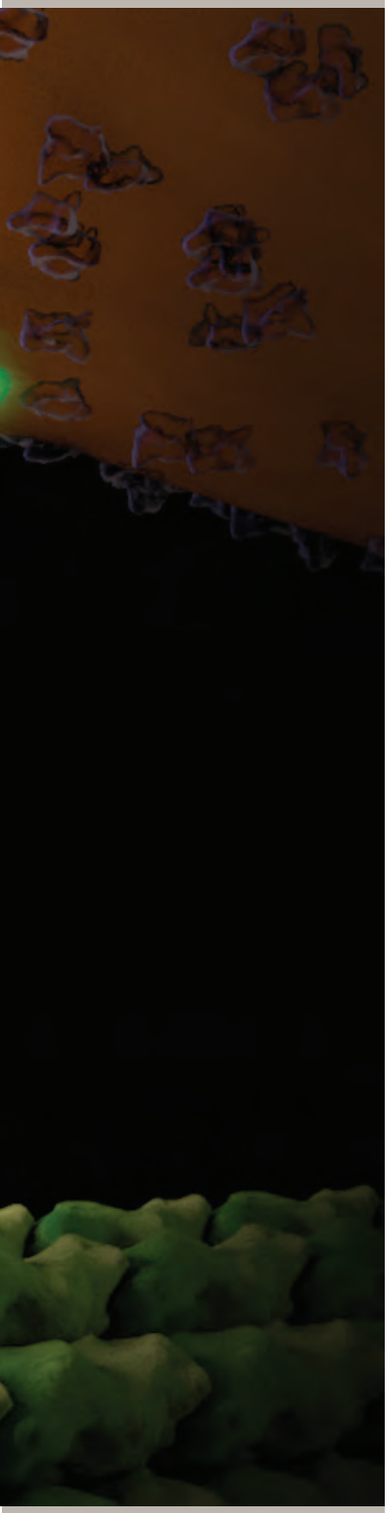
An advanced microscope reveals exciting biological surprises hidden to the eye

"This is this molecular motor that carries molecules along the interior of cells. Inside the cells we have these superhighways called microtubules. These are particularly important in neurons, which can be really long, up to a meter. To move something through a neuron you need some kind of a transporter. This molecule is involved in clearing out the junk from your neurons and bringing them back to cell bodies for destruction. It is critical for many functions, including cell division. Also, viruses hitch rides on these molecules to infect us."

–GABRIEL LANDER, PhD



LAB NOTES



One of the most exciting days in the career of structural biologist Gabriel Lander, PhD, at The Scripps Research Institute (TSRI) was the day he first saw the 3D structure of a chariot-like molecule involved in carrying key cellular cargo up and down the length of neurons through long, hollow cylinders called microtubules.

"The transporter that moves cellular cargo was discovered over 40 years ago, and for 40 years people have been trying to figure out how it moves," says Lander of TSRI's Department of Integrative Structural and Computational Biology. "We found out that it is built like a chariot pulled by horses, with one molecule holding together a team of other molecules so they all move forward together and carry large loads."

An advanced technology called cryo-electron microscopy (cryo-EM) made the discovery possible, and may help explain how malfunctions in these chariots contribute to neurological disorders. One of three faculty members running TSRI's cryo-EM facility, Lander has made many exciting discoveries about the structure of life. Here, he shares some of his favorite images, and explains how the technology works.

In 2017, the inventors of cryo-electron microscopy were awarded the Nobel Prize for Chemistry. Why is the technology so important to science?

GL: In order to understand what's happening in cells and how our cells are maintained, you have to understand how all the pieces of the cell work together. It's like going to a mechanic and saying, 'There's something wrong with my car.' Knowing how all the parts of the car work together enables the mechanic to fix the engine.

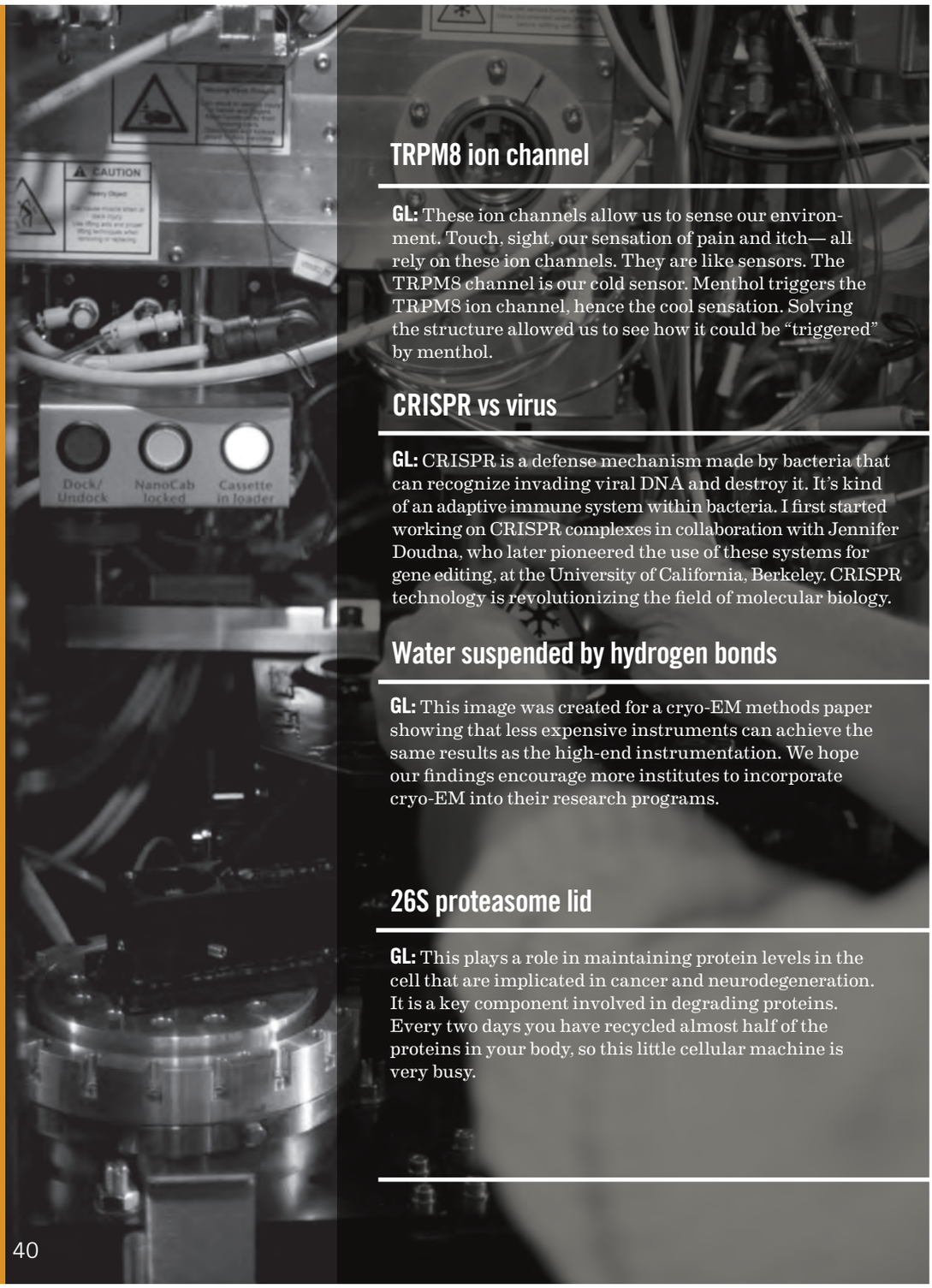
Several techniques have been used over the years to solve key molecular structures. The majority have been solved using x-ray crystallography, where you see the diffraction pattern of crystalized molecules but never actually look at the protein. It can take years, and in some cases the molecules never crystalize. Recent advances in cryo-EM now enable us to solve structures more quickly, with a similar degree of resolution as x-ray crystallography, but with the advantage that in cryo-EM we are literally looking at the molecules themselves. You can see an individual virus. You can also examine structures that are too flexible or too complicated to study with crystallography. It is absolutely wild. I am having a lot of fun.

Why do researchers need to understand the structure of key biological molecules?

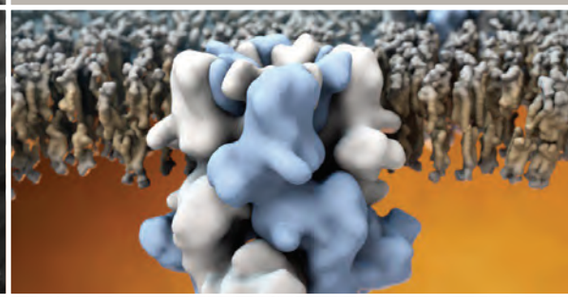
GL: The shape of a molecule has a lot to do with how it interacts with other molecules in your body. Think of it like a glove—your hand fits in it in one particular way. To treat diseases, you sometimes want to design a drug that fits into the shape of the binding pockets like a hand in a glove. Cryo-EM allows us to use computational methods to design molecules that fit into the pockets.

CRYO-EM IMAGES

Gabriel Lander, PhD, peers into the structures of the machinery of life. Here, he describes his recent discoveries.

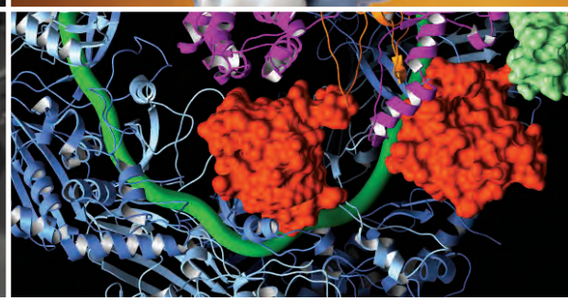


TRPM8 ion channel



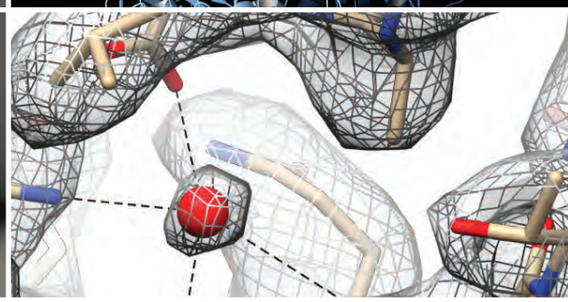
GL: These ion channels allow us to sense our environment. Touch, sight, our sensation of pain and itch— all rely on these ion channels. They are like sensors. The TRPM8 channel is our cold sensor. Menthol triggers the TRPM8 ion channel, hence the cool sensation. Solving the structure allowed us to see how it could be "triggered" by menthol.

CRISPR vs virus



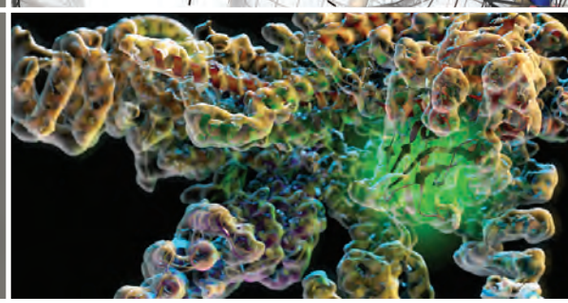
GL: CRISPR is a defense mechanism made by bacteria that can recognize invading viral DNA and destroy it. It's kind of an adaptive immune system within bacteria. I first started working on CRISPR complexes in collaboration with Jennifer Doudna, who later pioneered the use of these systems for gene editing, at the University of California, Berkeley. CRISPR technology is revolutionizing the field of molecular biology.

Water suspended by hydrogen bonds

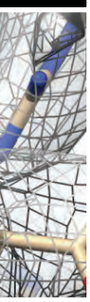


GL: This image was created for a cryo-EM methods paper showing that less expensive instruments can achieve the same results as the high-end instrumentation. We hope our findings encourage more institutes to incorporate cryo-EM into their research programs.

26S proteasome lid



GL: This plays a role in maintaining protein levels in the cell that are implicated in cancer and neurodegeneration. It is a key component involved in degrading proteins. Every two days you have recycled almost half of the proteins in your body, so this little cellular machine is very busy.



How do you select which molecules to study?

GL: I like to target molecules that have historically been too difficult to solve using other structural approaches—I love a good challenge. But we're also driven by a big biological question. I am very interested in how every cell accurately controls the generation and destruction of over a billion proteins within it. The cell is constantly making and destroying proteins, and any disturbance in this balance can lead to devastating diseases. I am really interested in seeing how this machinery works. For example, in a lot of the neurodegenerative diseases, including Huntington's, Alzheimer's and Parkinson's, neurons may be dying off because the protein levels aren't managed properly.

What's involved in capturing an incredible image like the ion channel that controls movement of molecules in and out of cells?

GL: It starts with a lot of biochemistry at the front end, which was done by our collaborator Seok-Yong Lee, PhD, at Duke. He sends us pristine, well-behaved protein complexes. He overnights it. The moment we get it, immediately we go to the cold room, where it's four degrees Celsius. We put a small amount, 3 microliters, on a 3-millimeter mesh grid. We use a piece of filter paper to absorb most of the sample and leave behind a thin layer on that grid. It plunges into liquid ethane cooled to minus-195 degrees Celsius. Super cold. That instantly freezes the sample, so fast the water molecules don't have time to rearrange and form crystals. Our particles are suspended in time, in this glass-like ice. We then take that frozen sample and put it into the electron microscope. The interior is a vacuum. The electrons come down at very close to the speed of light and interact with the sample to form an image, which is collected by a sophisticated camera at the bottom of the microscope. We then extract millions of data points from the images and use a series of complex processing algorithms to align them and solve the 3D structure of the molecule. I never imagined we'd be resolving structures with the level of detail we're seeing today.

Our facilities manager, Bill Anderson, has over 30 years of experience in electron microscopy. He does an exceptional job keeping the six microscopes we have at TSRI up and running.

What else do you want to do with cryo-EM?

GL: We want to look at these proteins in the cells themselves instead of breaking the cells open and extracting them. That would be the real holy grail. You don't know what happens to the proteins when you pull them out of a cell. It would be great to look at a healthy cell then look at a Parkinson's cell or a cancer cell, and see what is different inside. It could completely change the way we view certain diseases.



ENDOWING KNOWLEDGE

Graduate Program receives transformational gift from the Skaggs family

When you've chosen scientific research as your life's work, you'd like for that work to have an impact. Perhaps your insights will point the way along an untraveled path of discovery; perhaps they'll even lead to a novel medicine. The important thing is that you contribute to the centuries-long progression of scientific knowledge, informing and inspiring the next generation.

Acting on this thinking, faculty members at The Scripps Research Institute (TSRI) established a graduate school where they could help educate students pursuing doctoral degrees in chemical or biological sciences. The program they created in 1989 has since risen to national recognition and now, thanks to a lead gift by the Skaggs family, the faculty and students here have even more reason to celebrate.

A family dedication to education

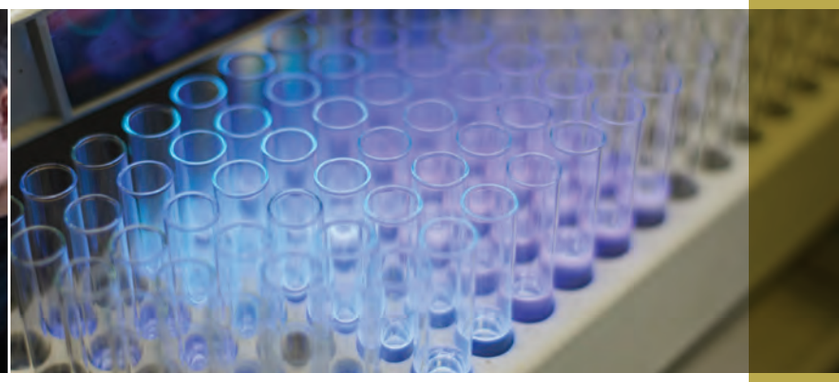
The Graduate Program at TSRI is receiving a transformational lead gift toward the Institute's $100 million campaign aimed at endowing fellowships for all students in perpetuity. That gift comes from two of the Skaggs family's foundations: the ALSAM Foundation and the Skaggs Foundation for Research. In recognition of this gift and the family's lifelong support of education at the Institute, the program will be renamed the Skaggs Graduate School of Chemical and Biological Sciences.

The Skaggs family's gift is helping others double their impact and make a difference, too. Donors who give $500,000 to the Graduate Program can now establish their own named $1 million fellowship, with the Skaggs gift contributing the additional $500,000. Phil Dawson, PhD, the dean of Graduate and Postdoctoral Studies, says the gift has inspired members of the faculty and Board to add their personal donations to the campaign, totaling more than $10 million to date. "We really value our students here at TSRI," he says. "Training the next generation of scientists is central to our identity."

Top 10 in the nation

For 18 straight years, *U.S. News & World Report* has listed TSRI's Graduate Program—which enrolls 40 to 50 students per year—among its top 10 Best Grad Schools





> "Students come from all over the world to study here. What they study, what they learn, what they discover and invent will impact the lives of millions."
>
> —RYAN SHENVI, ASSOCIATE PROFESSOR, TSRI GRADUATE PROGRAM

in the nation. More than 100 alumni currently hold faculty positions at major universities and colleges around the world and hundreds more have leadership roles in biotech and pharmaceutical companies.

A key feature of the Graduate Program is its interdisciplinary approach to education. Students have full access to all faculty regardless of department or specialty and can customize their curriculum to align with their own interests. By encouraging diverse training, TSRI's program equips its students with the ability to work knowledgably and creatively toward answering the world's most perplexing scientific questions.

For many of the graduate students, who are embarking on five years of intense study, the fellowships provided by the Skaggs family gift are a welcome relief from financial pressures. Expressing gratitude in a letter, one student wrote that the family donation "makes it possible for students like me to pursue my goal of becoming a research scientist." Another wrote that "as a result of the Skaggs fellowship, I can spend my time at work thinking about my next experiment." Ryan Shenvi, an associate professor in the Chemistry department and a Graduate Program faculty member, sums up the inestimable benefit of the gift: "Students come from all over the world to study here. What they study, what they learn, what they discover and invent will impact the lives of millions."

On the shoulders of giants

Sir Isaac Newton, one of the most influential scientists in the history of the world, once wrote: "If I have seen further it is by standing on the shoulders of giants." He acknowledged that his many successes sprang from the scientific thinking that preceded him. So it is at TSRI. The brilliant collective here—comprising what *Nature* calls "the most influential research institution in the world"—is training future scientific giants through our Graduate Program.

If you'd like to learn more about contributing to scientific history, to sustaining that critical, uninterrupted stream of knowledge, please contact our Philanthropy department, either in Florida or California. We'd love to welcome you as a recognized supporter of our Graduate Program endowment campaign.

RESEARCH UPDATE

In 2016, The Scripps Research Institute received a major award from the National Institutes of Health to lead key participant enrollment and research activities for the Precision Medicine Initiative's *All of Us* Research Program. The principal investigator is Eric Topol, MD, director of the Scripps Translational Science Institute and executive vice president of TSRI. Since founding STSI in 2006, Topol has been leading the charge to individualize and democratize health care through genomics and digital medicine.

Tackling such a monumental research effort takes a village. For an update on the program, *Endeavor* sat down with Katie Baca-Motes, MBA, program director of STSI's *All of Us* team, and Steven Steinhubl, MD, STSI's director of digital medicine.

Realizing individualized medicine for *All of Us*

What are the goals of the *All of Us* Research Program, and what is Scripps' role?

SS: The *All of Us* Research Program is the largest, most ambitious and visionary health-related research program ever undertaken. It will enable researchers, participants, and eventually the broader population, to better understand what makes all of us unique, and how our environment and our genes interact to either keep us well or make us unhealthy.

To achieve this, the program intends to enroll at least one million individuals living in America who reflect our nation's diversity, and then keep them engaged in the program for at least 10 years, and hopefully, decades beyond. Participants in the study will share biosamples for genetic and other testing, link their electronic health records to provide detailed, real-world longitudinal health information, take advantage of novel wearable sensors to track a variety of vital signs over time, and answer a series of surveys. Importantly, all the information obtained from participants will be returned to them.

KBM: The Participant Center at Scripps leads multiple components of the *All of Us* Research Program. First, we are responsible for the recruitment, enrollment and retention of people who are not served by participating healthcare provider organizations. These individuals, known as the "direct volunteers," will come from everywhere across the U.S. and its territories, and will primarily be engaged with all aspects of the program through digital means. We are working with a remarkable collection of partners to accomplish this, including Walgreens, WebMD, and the Blue Cross Blue Shield Association, among many others.

Second, we are helping lead the incorporation of wearable sensors and other digital technologies into the program. Early pilot programs include collaborations with Fitbit and Omron.

Beyond these two major components, we also lead the Support Center for the entire program, and through our sub-awardee, Sage Bionetworks, support protocol development and regulatory compliance.

What's happening at Scripps now to advance *All of Us*?

SS: The nationwide infrastructure necessary to successfully accomplish the goals of the program is enormous and complex. Although over 13,000 people have already enrolled as part of beta testing, the primary goals to date have been to develop the research infrastructure rather than carry out any large-scale research. The Scripps team of over 40 people dedicated to *All of Us* works closely with the NIH leadership, as well as the over 1,000 other members of the *All of Us* Research Program consortium to help make sure that the experience for future participants is as smooth, and ultimately, as valuable to them as possible.

Where does the *All of Us* Research Program fit into the bigger picture of the Precision Medicine Initiative?

KBM: The Precision Medicine Initiative was launched in 2016 as an investment by the NIH to accelerate biomedical research and provide clinicians with new tools to select the therapies that can be used in a more individualized approach with patients. The *All of Us* Research Program is the largest, but just one component of that. Another large component is the PMI-Oncology program that will use the genetics of cancer to identify effective and more precise therapies.

How can people participate?

KBM: Anyone who is interested can go to the website at www.joinallofus.org to learn more and sign up for program updates. Right now, we are accepting just a limited number of beta testers in certain areas. Later this spring, enrollment will open nationwide.

Making tomorrow a healthier place.

The extraordinary scientists at The Scripps Research Institute (TSRI) invest their talents every day to making tomorrow a healthier place to live for you and your loved ones.

The cross-disciplinary collaborations we pursue are pointing the way to novel and effective therpies, ones that focus on treating the disease and not just the symptoms. Additionally, our alliance with the California Institute for Biomedical Research (Calibr) is quickly transforming recent discoveries into new drugs. And our partnership with the Scripps Translational Science Institute is informing our progress toward true precision medicine.

High-risk, high-impact research such as this requires fearless ambition and substantial resources.

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Whether you wish to add your support to whatever need is greatest or direct it to studying a specific disease, please consider making a gift to The Scripps Research Institute. For more information, contact our Philanthropy department.

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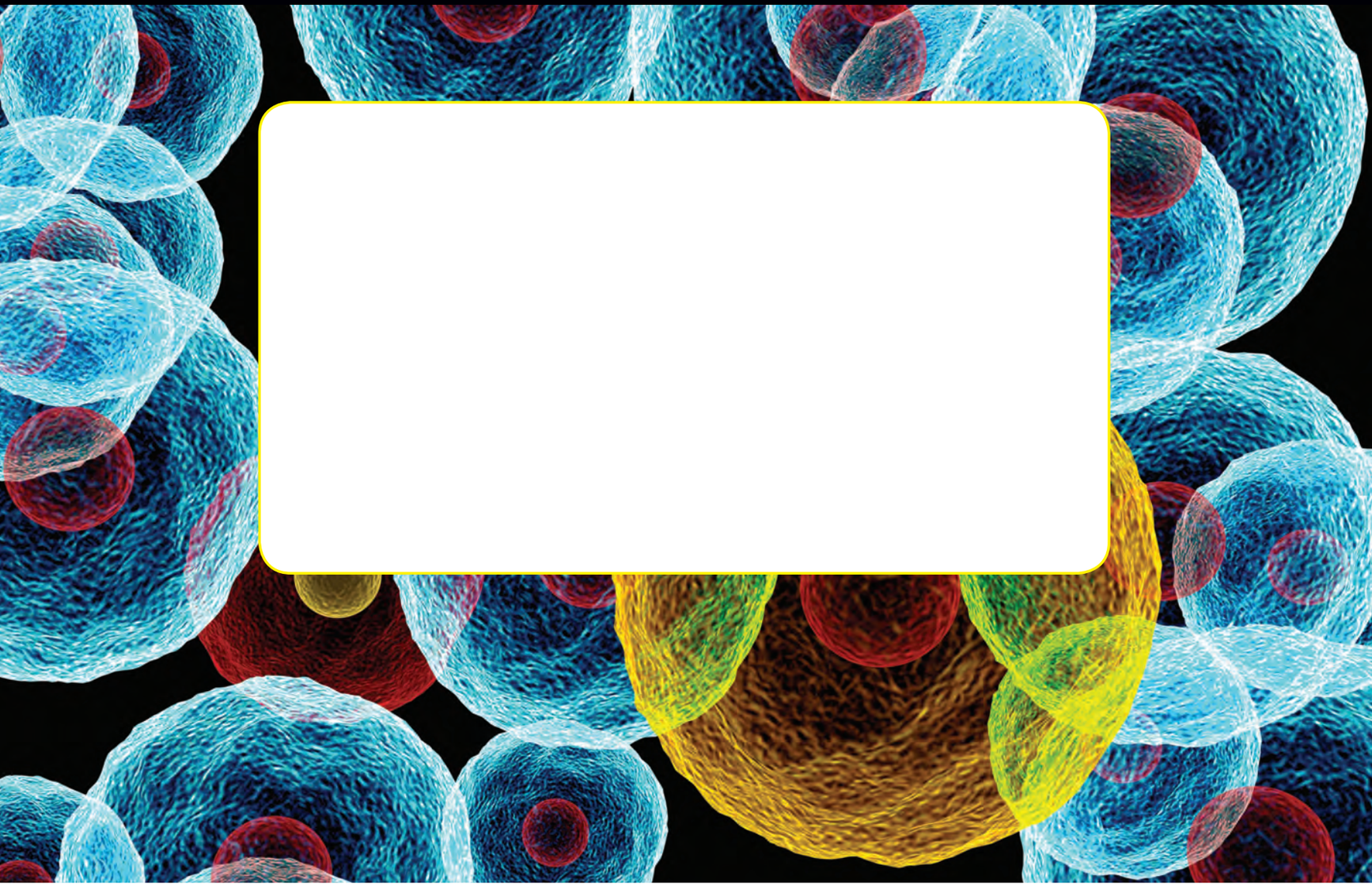

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