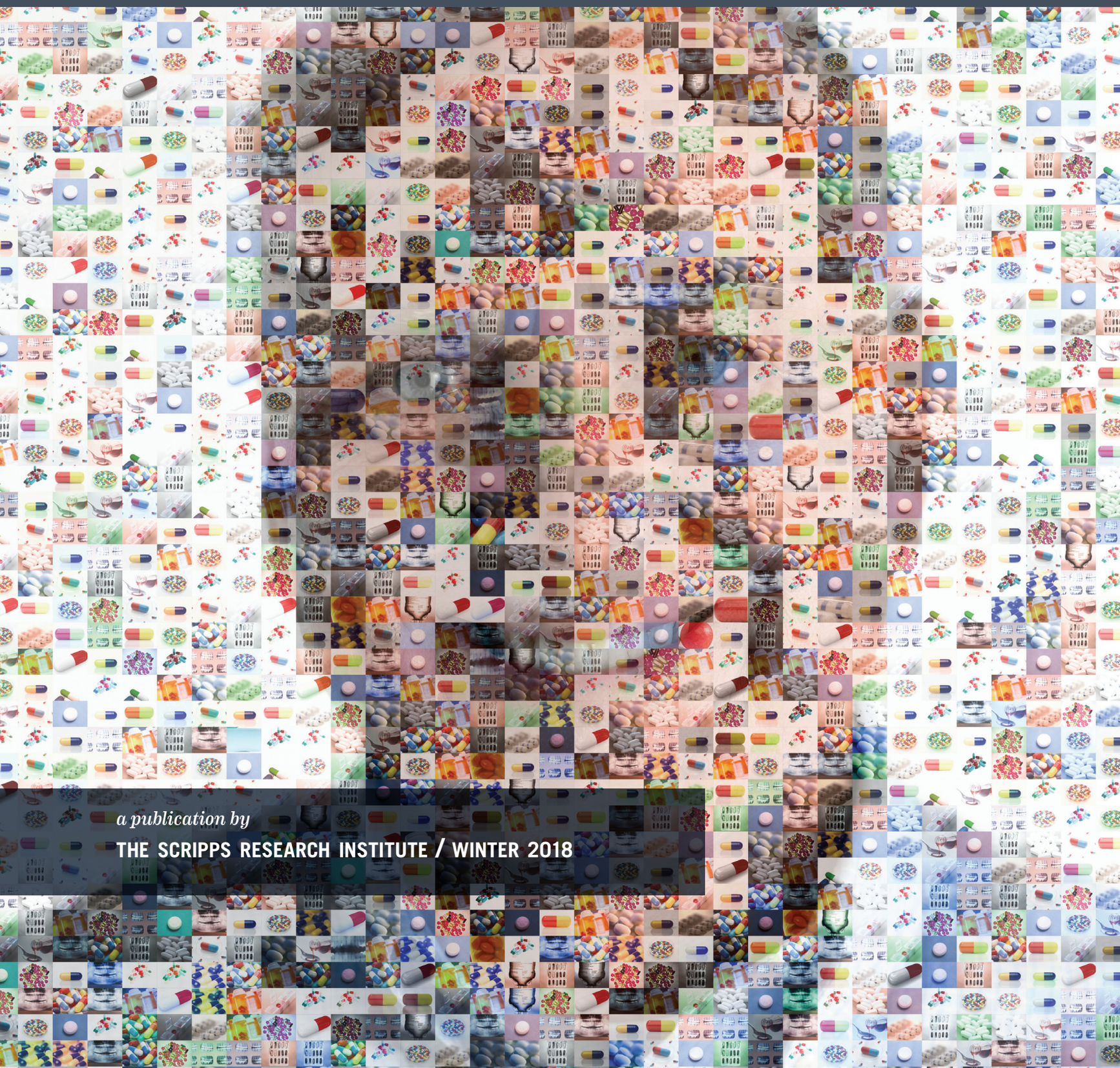
endeavor

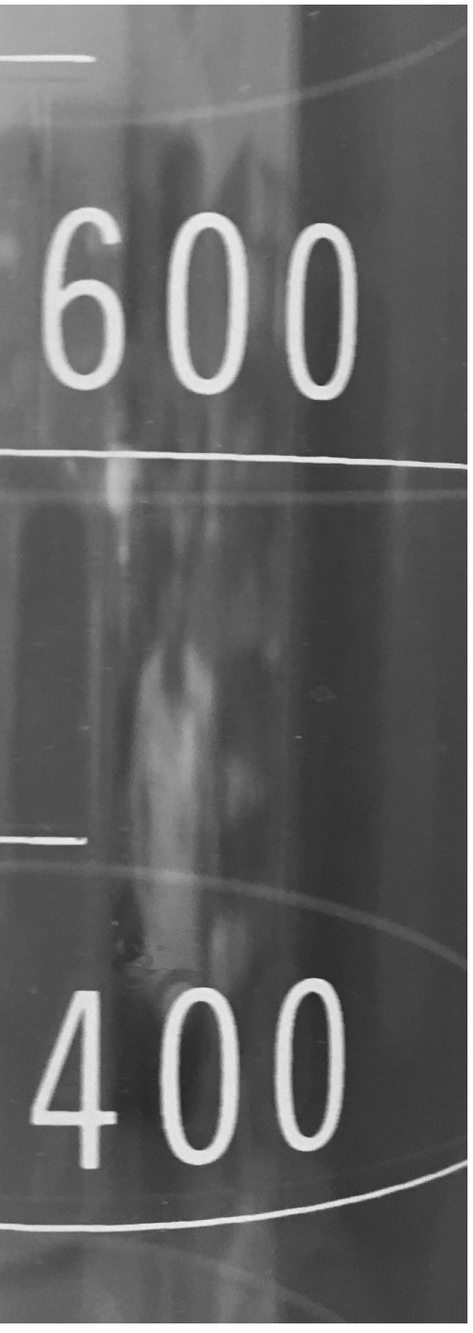
Nº 2



a publication by

THE SCRIPPS RESEARCH INSTITUTE / WINTER 2018


THE
SCRIPPS
RESEARCH
INSTITUTE



COVER IMAGE: Americans between 65 and 79 receive nearly 27 prescriptions per year, a recent study found. Are all those pills necessary? Understanding how individuals' genomic differences affect their specific health needs can lead to more efficient health care — high-definition medicine tailored to the needs of the individual. Scientists at the Scripps Translational Science Institute, part of The Scripps Research Institute, are using genomics, data science and biomedical research to advance a new era of democratized, individualized health care. Photograph by Thomas Northcut / DigitalVision Collection / Getty Images.

Letter from the President

Welcome to the second issue of *Endeavor,* a publication devoted to enlightening and inspiring you with stories of the scientific work underway at The Scripps Research Institute. Achieving our vision for scientific and strategic success has always depended upon your support, and on the many outstanding organizations and individuals we collaborate with every day. Together, we have achieved exciting things in 2017. We expect many more advances in the coming year.

A highlight of 2017 has been the recognition by our peers of TSRI's exceptional track record of influencing innovation. I have spent 18 years of my scientific career here, and I have long appreciated how curiosity and creativity drive our culture of innovation. Dogmas are challenged, original thinking flourishes, and entrepreneurialism thrives, as our scientists and students propel ideas into discoveries that change lives and science. So it was especially gratifying when the eminent scientific journal *Nature* objectively ranked TSRI first worldwide for influence on innovation, ahead of 200 other universities and research organizations, in its annual *Nature Index 2017 Innovation* supplement. Based on publications cited in third-party patent applications, TSRI ranked ahead of internationally renowned institutes including The Rockefeller University, the Massachusetts Institute of Technology and Stanford University. With more than 1,000 patents and seven FDA-approved medicines to our credit, the scientists of TSRI set the standard for innovation excellence.

Among the innovators highlighted in this issue, you will meet Patrick R. Griffin, Ph.D., co-chair of the TSRI Department of Molecular Medicine. Griffin finds the structure of important biological molecules using innovative methods, drawing inspiration from his dives through Florida's underground network of caves. You will also meet Neuroscience Professor Kristin Baldwin, Ph.D. Her work reprogramming mature cells back to their pluripotent stem-cell state offers new insights in the study of the diseases of aging and more.

Looking ahead, we greet another milestone in the history of TSRI. A formerly affiliated partner, the Scripps Translational Science Institute, founded by renowned cardiologist Eric Topol, M.D., has become an institute within TSRI. Dr. Topol sees clearly how advances in mobile technology, data science, genomics and bioscience can change medical care for the better. As a recipient of one of the largest grants in the history of the National Institutes of Health, he helps lead the *All of Us* research program, which seeks to engage a million or more participants in a historic effort to transform medical care. Together with the drug-discovery skills of another TSRI partner, the California Institute for Biomedical Research (Calibr), we now have the unique potential to not only discover the drivers of human diseases, but to find and advance their treatments.

Perhaps the most important pages of this issue of *Endeavor* are those introducing you to the visionary supporters of TSRI who give year after year, sustaining the groundbreaking research that drives innovation. Contributions from devoted individuals including Celia Lipton Farris, Florence Dembling, Helen Dorris, Ellen Browning Scripps, and many, many more, have made TSRI the engine of discovery, education and innovation that it is today.

On behalf of all the faculty, staff and students of TSRI,
we sincerely thank you.

PETE SCHULTZ, PH.D. / PRESIDENT, TSRI

Board of Directors

Chairman John D. Diekman, Ph.D.
Founding Partner, 5AM Ventures

Herb Boyer, Ph.D.
Co-Founder, Genentech

Ron Burkle
Founder, The Yucaipa Companies;
Founder and Chairman,
Ronald W. Burkle Foundation

Gerald Chan, Ph.D.
Co-Founder, Morningside

Mark Edwards
Founder, Bioscience Advisors, Inc.

Peter C. Farrell, Ph.D., D.Sc.
Founder and Chairman, ResMed

Isy Goldwasser
Co-Founder and CEO, Thync, Inc.

William R. Hearst III
Chairman, Hearst Corporation

Ge Li, Ph.D.
Founder, Chairman and CEO,
WuXi AppTec

Claudia S. Luttrell
President, The Skaggs Institute
for Chemical Biology

Joel Marcus
Founder, Chairman and CEO,
Alexandria Real Estate Equities, Inc.

Mark Pearson
Co-Founder and Vice Chairman,
Drawbridge Realty Trust

Bernard Saint-Donat, Ph.D.
President, Saint-Donat & Co.

Peter G. Schultz, Ph.D.
President and Vice Chairman,
The Scripps Research Institute

Christopher T. Walsh, Ph.D.
Consulting Professor to the Stanford University
Department of Chemistry

Faculty Board Appointee
Paul Schimmel, Ph.D.
Hahn Professor in the Department
of Molecular Medicine and Chemistry,
The Scripps Research Institute

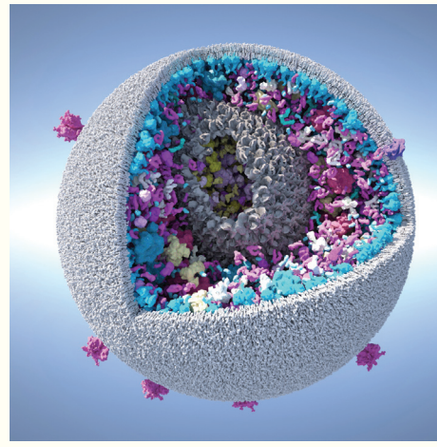
NEWS HIGHLIGHTS

TSRI Ranks No. 1 in Worldwide Influence

TSRI is the most influential research institution in the world, according to a recent analysis by the *Nature Index*. The "innovation" ranking is determined by data on research quality and the broad influence the institute has on inventions. "This new ranking underscores the worldwide impact of TSRI scientists, who share a common goal of improving public health through scientific discovery, and, importantly, improving the way we make those discoveries," said Jamie Williamson, Ph.D., TSRI's executive vice president for research and academic affairs. "We are proud to be recognized for the profound influence our science has had on other researchers and laboratories."

HIV Vaccine and Treatment Research Moves Forward

Researchers on the TSRI California campus recently found that HIV vaccine candidate molecules elicit antibodies against HIV in calves. This is a key step in developing a vaccine in humans. A second project shed light on the best ways to deliver an HIV vaccine by testing vaccine candidates set to go into humans in 2018. On the Florida campus, a team led by Susana Valente, Ph.D., discovered that HIV viral production can be blocked in chronically infected cells with an experimental drug treatment — what the lab calls a "functional cure" for the disease.



A MODEL OF HIV CUT AWAY TO SHOW THE INTERIOR OF THE VIRUS. IMAGE BY THE OLSON LAB.

Anti-Heroin Vaccine Delivers Results

Opioid addiction researchers at TSRI recently announced that an experimental anti-heroin vaccine works in non-human primates. The vaccine blocks heroin drug molecules from reaching the brain to cause a "high"— potentially removing the temptation for recovering addicts to relapse. "We believe this vaccine candidate will prove safe for human trials," said study leader Kim Janda, Ph.D., the Ely R. Callaway Jr. Professor of Chemistry and member of the Skaggs Institute for Chemical Biology at TSRI.

DIGIMED17: Transforming Healthcare Through Digital Medicine

In October, the Scripps Translational Science Institute (STSI) hosted a two-day conference focusing on the clinical evidence necessary to drive the uptake of digital health solutions. Speakers from organizations including Fitbit, IBM, Google, Stanford University and Oxford University discussed wearable biosensors, soft sensors, virtual care, robotics, machine learning and more. Scott Gottlieb, M.D., commissioner of the U.S. Food and Drug Administration, delivered the keynote address. "The principal goal of the conference is to jumpstart efforts to drive the widespread incorporation of evidence-based digital medicine solutions for more-personalized, individual-centric care" said conference director Steven Steinhubl, M.D., Director of Digital Medicine at STSI.

AWARDS, GRANTS + HONORS

The HIV Interactions in Viral Evolution (HIVE) Center at TSRI has been awarded nearly $27 million from the National Institute of General Medical Sciences of the National Institutes of Health (NIH). This continues the crucial work by the HIVE Center and HIVE co-director **Bruce Torbett, PhD.**, to study HIV at the atomic level on both TSRI campuses.

Researchers at TSRI in Florida, led by **Paul Robbins, Ph.D.**, director of the TSRI Center on Aging, and Albert Einstein College of Medicine, will share in a $9 million grant from the NIH's National Institute on Aging to study how individual genetic differences may form the basis for new therapeutic approaches that target the aging process.

Staff Scientist **Kathryn Hastie, Ph.D**., won the 2017 William E. and Diane M. Spicer Young Investigator Award of Stanford Synchrotron Radiation Lightsource for her research on Lassa virus, a pathogen that infects hundreds of thousands of people each year.

Immune system researchers on the California campus, led by Professor **Richard J. Ulevitch, Ph.D.**, have been awarded a five-year, $11.2 million grant from the NIH's National Institute of Allergy and Infectious Diseases to study the detailed workings of the mammalian immune system.

The prestigious National Academies of Science, Medicine and Engineering honored three TSRI scientists. **Phil Baran, Ph.D.**, the Darlene Shiley Professor of Chemistry at TSRI, and **Ardem Patapoutian, Ph.D**., a member of the Dorris Neuroscience Center at TSRI and an investigator with the Howard Hughes Medical Institute, were elected to the National Academy of Sciences. Co-Chair of the Department of Molecular Medicine **Benjamin Cravatt, Ph.D.**, was elected to the National Academy of Medicine.

A team of Scripps Florida scientists led by **Gavin Rumbaugh, Ph.D**., has been awarded nearly $2 million from the NIH's National Institute of Mental Health to develop an industrial-level high throughput screening platform that could lead to new treatments for a number of childhood brain disorders.

Matthew Disney, Ph.D., together with scientists from Mayo Clinic's Florida campus and Johns Hopkins School of Medicine, has been awarded $7.2 million from the NIH's National Institute of Neurological Disorders and Stroke to create new RNA-based treatments for the most common form of amyotrophic lateral sclerosis (ALS), as well as a type of frontotemporal dementia (FTD).

Together with Brigham and Women's Hospital, **Patrick Griffin, Ph.D.**, co-chair of the Department of Molecular Medicine on the Florida campus of TSRI, has been awarded a $2.5 million collaborative grant by the NIH's National Institute of Diabetes and Digestive and Kidney Diseases to study whether the inhibition of a particular protein might be a viable target in the treatment of type 2 diabetes.

Matt Tremblay, Ph.D., chief operating officer of the California Institute of Biomedical Research (Calibr) and vice president of business development at TSRI, has been named one of Biocom Inc.'s annual Life Science Catalyst Award winners.

Keary Engle, Ph.D., has been awarded a $1.25 million grant from NIH's National Institute of General Medical Sciences. The grant, also known as an "Outstanding Investigator Award" and "Maximizing Investigators' Research Award (MIRA) for Early Stage Investigators," will support the Engle Laboratory's development of powerful new molecule-building techniques for drug discovery.

TOP: ERICA OLLMANN SAPHIRE AND KATHRYN HASTIE.
BELOW: KEARY M. ENGLE.

MINING DATA TO IMPROVE MEDICAL CARE: STSI'S ALI TORKAMANI, STEVEN STEINHUBL, ERIC TOPOL AND KATIE BACA-MOTES. DATA SENT BY WIRELESS DEVICES INCLUDING PULSE OXIMETERS, WHEN COMBINED WITH GENOMICS AND OTHER HEALTH INFORMATION, MAY HELP SCIENTISTS DEVISE MORE PRECISE CARE GUIDELINES.

Partners in Precision

MINING DATA TO IMPROVE MEDICAL CARE

His patient's email arrived with an urgent subject line: "I'm in atrial fib, now what do I do?"

Not only had Eric Topol, M.D.'s patient used a smartphone to record data about his irregular heart rhythm, he used its app to correctly interpret the results, something the eminent cardiologist had spent many years learning. After responding to his patient's concerns, Topol paused and considered the enormity of the moment. At a time when three of four people on the planet had such phones — when personal fitness trackers were on every wrist at gyms — Topol realized his dream of democratized health care had begun.

"In our unplugged world full of mobile devices, a diagnosis could now be made anywhere, anytime, by anybody. Or by a machine," he writes in his book, "The Patient Will See You Now: The Future of Medicine."

"The ability to share data and contextually compute it led the nonmedical world to progress many could not have even imagined, leading to advances like driverless cars," he writes. "The shake-up of medicine will be just as strong."

Topol is helping lead medicine's shake-up. The director of the Scripps Translational Science Institute (STSI) at The Scripps Research Institute (TSRI), Topol — cardiologist, professor of genomics, and medical futurist — sees clearly how to harness technology to change both the practice and culture of medicine for the better. The flood of personalized data can transform one-size-fits-all "average" care into something extraordinarily important: high-definition, individualized, immediately available health care, Topol says.

by

STACEY SINGER DELOYE + BONNIE WARD

It's a collaboration of giants.

Achieving that dream requires the collaboration of the best minds in many disciplines: health care, genomics, data science, chemical biology and pharmacology, Topol says. He has found that rare combination of talent atop San Diego's Torrey Pines Mesa, where STSI researchers work alongside scientists at Scripps Research and the affiliated California Institute for Biomedical Research (Calibr).

It's a collaboration of giants.

Top-tier scientific journal *Nature* recently ranked Scripps Research No. 1 in the world for the quality and impact of its groundbreaking research, particularly in chemistry, synthetic biology, HIV and Ebola, ahead of much larger institutions.

Topol's STSI, meanwhile, is developing a new precision paradigm for medical care delivery, one that's patient-empowered and tailored to the individual, employing advances in genomics, computing, imaging and mobile bio-tracking. Topol himself has been called the most influential physician in America.

At Calibr, state-of-the-art drug discovery expertise and unique tools rival those of large pharmaceutical companies, enabling more efficient translation of scientific breakthroughs into new medicines.

"The intersection of basic life science and medicine is now center stage," Topol says speaking from his office on the La Jolla, California Torrey Pines Mesa. "We are at a unique time in medicine, where transdisciplinary efforts will be required to not only free and amass the data, but also to maximize its value."

To that end, he is restructuring his 10-year-old institute by flipping the relationships between STSI, Scripps Research and clinical provider Scripps Health.

Under the new structure, the Scripps Translational Science Institute will become part of The Scripps Research Institute, working closely with Calibr, which shares senior leadership with Scripps Research. Topol said STSI will maintain its partnership with Scripps Health, including a major collaboration under the Clinical and Translational Science Award NIH grant, with Scripps Health as the clinical partner.

"Now our mission is much bigger. Our role is to serve as an individualized medicine hub, with patient interest at heart," Topol says.

The evolving partnership braids together the unique strengths of all three institutes, to the benefit of patients, says Peter Schultz, Ph.D., president of TSRI and founding CEO of Calibr.

"This alliance enables clinicians at STSI to keep pushing when traditional medicine runs out of answers," Schultz says. "And it enables

PRECISION MEDICAL CARE MEANS MEDICAL CARE TAILORED TO THE INDIVIDUAL. 1. BRAIN SENSING ELECTROENCEPHALOGRAM — EEG, 2. PORTABLE COLPOSCOPY AND 3. VITAL SIGN SCANNER TO COLLECT AND SEND IMPORTANT DATA

scientists working on fundamental questions of biology to look to patients themselves for genetic and epigenetic direction. We bring in the expertise at Calibr to find and develop discoveries into treatments for disease. It's a powerful partnership at an incredible moment in science and technology."

Topol says there will be many important areas of collaboration, among them, solving the mysteries of unknown diseases and taking the next step — seeking out effective treatments from among more than a million biologically active compounds and antibodies housed within the research laboratories of TSRI and Calibr.

"We have over 75 families where at least one member has had an unknown disease. They have spent years on a so-called diagnostic odyssey, and up to millions of dollars of charges, and they still don't know what's wrong with them," Topol says. "We can sequence the genomes of that person and their family and we can understand what it is. But doctors can't fix the problem, typically, because they can't make a drug. At TSRI we have scientists throughout the institute who can do that."

"Now our mission is much bigger. Our role is to serve as an individualized medicine hub, with patient interests at heart."

1

2

3

His inspiration for the initiative has come from patients themselves, especially Bertrand Might, a young boy born with a rare disease that leads to seizures, loss of muscle tone, developmental delays and liver damage. His father, Matt Might, using social media, found eight other families whose children suffered the same condition. Through genetic sequencing, they learned the common source of the condition was a gene called NGLY1. Now, researchers and doctors are helping to test potential treatments. When patients gain power over their own medical information, great and important things happen, Topol says.

That's a core value of another important research focus of STSI and Scripps Research, the *All of Us* research program, part of the national Precision Medicine Initiative (PMI), launched by the National Institutes of Health (NIH). The NIH awarded Topol and Scripps Research a $207 million grant — the largest NIH grant in Scripps Research history — to pursue what's been called one of the most ambitious medical research efforts in U.S. history.

The PMI's *All of Us* research program is broken down into several sections. The Participant Center, led by STSI, is charged with enrolling 350,000 of 1 million U.S. volunteers to generate and assess their individual health data. Enrollment will soon begin, said Katie Baca-Motes, the Center's director. She says participants will be treated as research partners and given access to the study's results. A broad cross-section of volunteers will be included, she adds.

"This is going to be the largest longitudinal study that's ever been done in this country," she says.

The hope is that the treasure trove of real-life health information will enable the prevention and better management of disease.

Topol and his team are also tasked with integrating mobile apps and digital medical devices into the program and the resulting research studies. The ultimate goal is what Topol describes as "High-Definition Medicine" in a new paper recently published in the journal *Cell* with his colleagues Ali Torkamani, Ph.D., Kristian Andersen, Ph.D., and Steven Steinhubl, M.D.

"Current medical tests often rely on coarse-grained, static and often isolated snapshots of an individual's health state taken months or even years apart," the authors write.

"More comprehensive representation of patient characteristics with high-definition medicine technologies will allow for a truly predictive and preventative health care system," they write.

The approach represents a monumental shift from today's one-size-fits-all method, where most medical treatments work well for some people but not others, Topol says.

A A C A A G T T A A T A A A C T A A A A C T T T C A A C A A C G G A T C T A A A C A A G T T A A T A A A C T A A A A C T T T C A A C A A C

THE TSRI HIGH PERFORMANCE COMPUTING CLUSTER ENABLES STORAGE AND ANALYSIS OF LARGE DATA SETS SUCH AS HUMAN GENOMIC DATA.

APPLYING THE TOOLS OF COMPUTER SCIENCE AND STATISTICS TO THE PURSUIT OF BIOMEDICAL DISCOVERY IS TRANSFORMING MEDICINE.

TAATAAACTAAAACTTTCAACAACGGATCTAAACAAGTTAATAAACTAAAACTTTCAACAACGGATCTA

"The more we understand about individual differences, the better able we will be to effectively prevent and treat illness."

Participants in the *All of Us* program will be invited to answer questions about their health history and status, share their genomic and other biological information and grant access to their clinical data from electronic health records. Mobile devices, such as wearable sensors, smartphone applications and other digital medicine devices, will play a big role, providing data in real time.

The initial study will run for five years after which the data will be centrally deposited with Vanderbilt University, another partner, and then analyzed to gain medical insights. Researchers hope they will be able to follow participants even longer, perhaps for decades. NIH Director Francis S. Collins, M.D., Ph.D., in a 2016 news release, said information will help answer important health questions such as why some people at high risk for certain diseases remain healthy, and how others with chronic diseases can maintain the best possible quality of life.

"This range of information at the scale of 1 million people from all walks of life will be an unprecedented resource for researchers working to understand all of the factors that influence health and disease," Collins said. "The more we understand about individual differences, the better able we will be to effectively prevent and treat illness."

As the data accumulates, Topol expects it will slowly change the way health care is delivered, much like the famed 1948 study that followed more than 5,000 residents of Framingham, Massachusetts for decades to identify cardiac risk factors. "We learned more about heart disease in that one study than any other study ever," said Topol. "Before that time, we didn't even know that smoking contributed to heart disease."

But this advance will be different. This time, patients themselves will own their health data, and over time they will be able to see where their data falls into the bigger picture of people like them. Initiatives like this will drive change in medicine, Topol predicts.

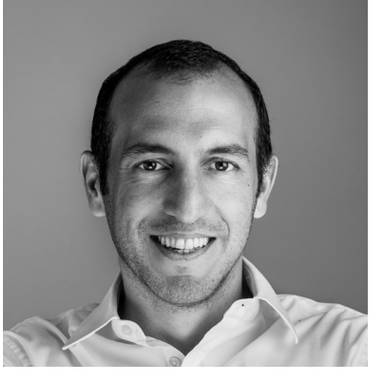
"As in every other sector of our lives, when data becomes eminently portable and granular, when there's so much more of it and it's free flowing, fully transparent, and there's seemingly unlimited computing power to process it, historic change takes place," Topol writes in "The Patient Will See You Now."

The collaborative, cross-disciplinary culture of inquiry and insight at Scripps Research provides the ideal climate for learning from "the wisdom of the population," he writes.

"The lack of boundaries between academia, the life sciences industry and the information technology sectors is just what is needed to tap into the boundless potential," he writes. "To say 'it takes a village' would be an extreme understatement. But when accomplished, this will get us to the wisdom of the population."

AACAAGTTAATAAACTAAAACTTTCAACAACGGATCTAAACAAGTTAATAAACTAAAACTT

THE POWER OF GENOMICS IN MEDICINE



ALI TORKAMANI, KRISTIAN ANDERSEN AND EMILY SPENCER USE GENOMIC DATA IN THEIR RESEARCH.

A SINUS RHYTHM, THE EBOLA VIRUS AND AN ILLUSTRATION OF HEART DISEASE. NEW SOURCES OF HEALTH DATA ARE DRIVING DISCOVERIES IN MEDICINE.

Genomic sequencing — which allows researchers to decipher an individual's biological blueprint — offers one of the most powerful tools in advancing individualized medicine. While its use is gaining ground in certain medical specialties, such as cancer, it remains a largely untapped resource. One of STSI's main missions is to expand genomics use by doctors and patients in the broader medical community — a goal it is advancing through innovative research and education. Some examples of STSI's work in this area include:

Heart Disease

Ali Torkamani, Ph.D., STSI's director of genomics and a TSRI associate professor, is using genomics, coupled with smartphone technology, to help people better understand their risk of coronary heart disease and how they can improve their heart health.

MyGeneRank is a smartphone application developed by STSI that is freely available for download by iPhone users. Anyone who has had genetic profiling through 23andMe, a direct-to-consumer genetic testing service, can consent to be part of a social genomics project using MyGeneRank, where the app will calculate a coronary artery disease polygenic risk score and provide participants their cardiac risk ranking and long-term risk for heart attack based on a combination of clinical, genetic, and lifestyle risk factors.

"The thinking is that if you more precisely know your risk, you may be more motivated to reduce your risk through healthy behavior," said Torkamani. Participants will receive information on ways to improve their health and get periodic follow up to determine if risk awareness positively influences health-related behaviors.

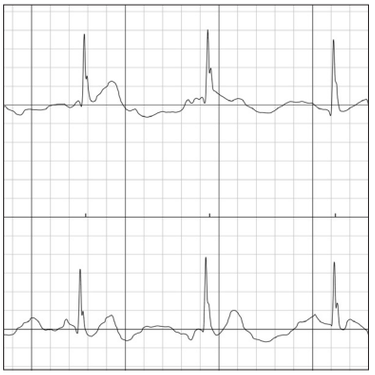
Infectious Diseases

Viruses, like people, have genomes. Kristian Andersen, Ph.D., STSI's director of infectious disease genomics and a TSRI assistant professor, has used that knowledge to great effect against some of the world's most dangerous pathogens, including the Zika and Ebola viruses.

Last year, Andersen led a large international team that used genomic sequencing to map Zika virus's entrance into the United States via Florida and then tracked its movement through tiny changes in its genome sequence. Such information, which he quickly made publicly available, can aid researchers around the world working on a vaccine, and help public health control efforts by showing how the virus is spreading.

One of STSI's main missions is to expand genomics use by doctors and patients in the broader medical community – a goal it is advancing through innovative research and education.

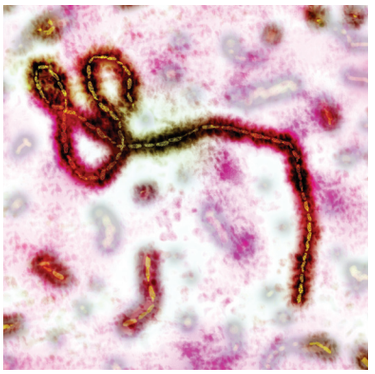
With the deadly Ebola virus, Andersen's intricate knowledge of viral genomics enabled him to create a diagnostic blood test for Ebola. The test was used during the outbreak in Sierra Leone, West Africa in 2014 and enabled medical workers to confirm the first Ebola cases in Sierra Leone and Nigeria.



Sudden Death

Torkamani is also involved in a novel project to use genomics to better understand unexplained deaths. "We're talking about healthy people who pass away suddenly and unexpectedly," said Emily Spencer, Ph.D., director of STSI's clinical genomics research program, who also works on the project.

Working with the San Diego County Medical Examiner, and with permission from families, STSI researchers perform "molecular autopsies" to seek an explanation for the individual's sudden death. The researchers have found genetic causes, abnormal heart rhythms and other factors. "Even in the cases where we ultimately find no explanation, grieving families tend to respond positively to the opportunity to identify a genetic cause of sudden death," said Torkamani.



In other instances, particularly with the sudden death of an infant, pinpointing the cause can be comforting. "The family may feel like they did something wrong that led to the sudden death," said Torkamani. "This knowledge can provide a sense of relief."

Understanding unexplained deaths can also be important for the health of relatives. For instance, knowledge that a relative died due to an abnormal heart rhythm can alert family members to be tested for similar issues and, if discovered, begin protective measures.

RESEARCHERS AT STSI ARE TRYING TO UNLOCK THE GENETIC SECRETS BEHIND LIFELONG HEALTH. THESE STUDY PARTICIPANTS ARE PART OF A "WELLDERLY" COHORT OF MORE THAN 1,400 PEOPLE AGES 80 TO 105 WHO HAVE NOT DEVELOPED ANY COMMON CHRONIC MEDICAL CONDITIONS.

> "J'ai jamais été malade, jamais, jamais." (I have never been ill, never ever.)
>
> — JEANNE LOUISE CALMENT

Aging Gracefully

IN PURSUIT OF SUPERIOR HEALTHSPAN

Frenchwoman Jeanne Louise Calment lived for more than 122 years, enjoying her daily café au lait and sweets. Yet somehow, she never experienced a major illness, even until her death 20 years ago.

Indonesian elder Mbah Gotho walked without a cane until the year before his death. His ID card put his age at 146, though many experts cast doubt on that figure. Likewise, he told The Jakarta Post he had never experienced a serious illness.

Whether Gotho's birth date is confirmed, the observation that exceptional longevity goes hand-in-hand with exceptional, lifelong good health is of great interest to scientists. It points toward protective genetic and environmental factors which can be capitalized upon to improve the "healthspan," or years of disease-free life.

"Aging is the number one risk factor for multiple chronic diseases," says Laura J. Niedernhofer, M.D., Ph.D., of TSRI's Department of Molecular Medicine. "That's why it make sense to therapeutically target aging itself."

by

STACEY SINGER DELOYE

RESEARCH COLLABORATORS LAURA J. NIEDERNHOFER AND PAUL D. ROBBINS. PHOTOS BY LILA PHOTO.

On both the Florida and California campuses of TSRI, teams of scientists are making groundbreaking discoveries about aging and its diseases, moving them efficiently toward clinical trials in collaboration with the affiliated California Institute for Biomedical Research (Calibr), and Scripps Translational Science Institute (STSI). Fundamental research about cellular metabolism, growth, senescence and death is combined with state-of-the-art drug investigation platforms to translate discoveries into therapies — both for diseases of aging, such as arthritis and Alzheimer's, and also possibly for aging itself.

The average lifespan of Americans has benefited mightily from the medical and public health advances of the 20th Century — increasing from 47.7 in 1900 to almost 80 today. Yet our healthspan, the years of good health and function, hasn't fared as well.

"Aging is not a disease. It is a natural process. But we have to start treating it like a disease."

In Niedernhofer's bright white office, neatly stacked papers cover most surfaces. Partially written articles and grant proposals sit alongside her keyboard. Behind her, a tall reading stack interrupts her line of sight to the labs where her extraordinary mice live.

Niedernhofer's mice grow old quickly. Bred to lack a critical DNA-repair gene called ERCC1, in just six months, the mice develop aging characteristics typical of senior mice — sagging, wrinkled skin; hair loss, and muscle weakness.

"They go blind and deaf; they get diabetes, dementia and cancer," she says. "Which allows me to conduct anti-aging studies in months rather than years."

A few doors down, Paul D. Robbins, Ph.D., her collaborator and partner, faces the same partially written articles and grant applications — but on his computer. A professor of molecular medicine at TSRI's Jupiter campus, Robbins is looking for — and finding — drug-like compounds that appear capable of delaying the onset of multiple aging-associated ailments.

Robbins and Niedernhofer moved to TSRI together in 2012, because of its world-class drug discovery tools, talented chemists and an openness to their ideas. By 2015, they were collaborating with researchers from the Mayo Clinic and the University Medical Center Groningen (in the Netherlands) to seek drugs that might affect aging diseases. The screening work done at TSRI produced important hits on a target identified at Mayo.

The compounds they identified, described in the journal *Aging Cell*, included an anti-cancer drug already on the market called dasatinib, and a natural plant pigment found in capers, kale and apple skins, called quercetin. Tested in Niedernhofer's and other aging mice, the drugs seemed to turn back the clock on many conditions. The compounds proved even more effective when administered together.

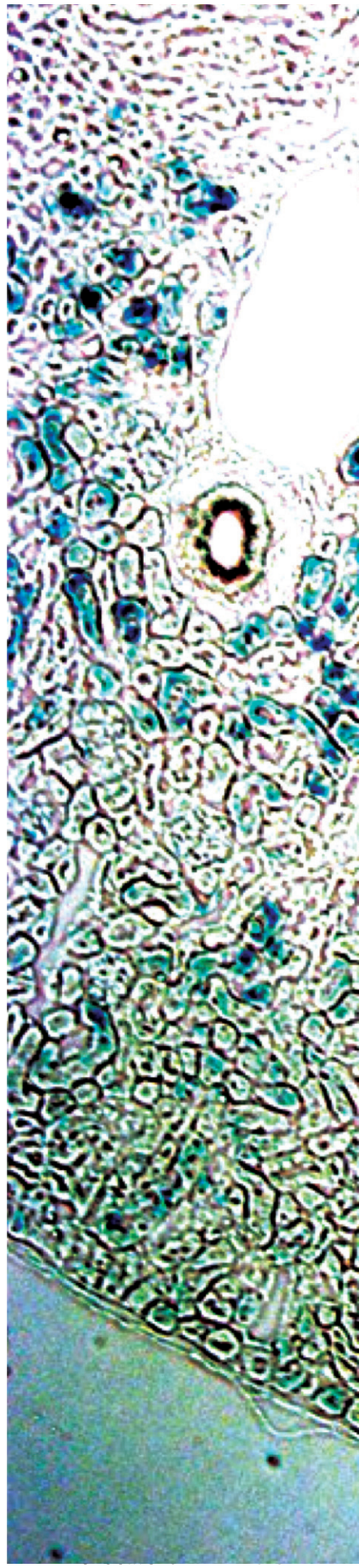
Referred to as "senolytics," the compounds target "senescent" cells. Such cells are the damaged zombies of the body. They no longer divide, but they also don't die. Senescence has the useful quality of preventing malignant tumor growth, but at a steep price. Senescent cells are "angry," churning out pro-inflammatory, cell-destroying factors all around the tissue in which they live. The "living dead" cells accumulate as we age, causing damage to the nearby healthy tissue.

"The accumulation of these cells drives what's called 'sterile inflammation,' which gives you creaky joints, bad responses to vaccinations, the things you associate with aging," she says.

The duo are currently studying the potential of other powerful senolytic substances, including a pair of anti-cancer compounds called BCL-XL inhibitors, and fisetin, a plant pigment found in strawberries, apples, cucumber skins, red onions and mangoes. The compounds enable the cells to restart their natural self-destruct programs. They may also have applications for dementia, although more research is required.

New thinking on Alzheimer's is clearly needed. Despite the fact that an estimated 30 million people globally have been diagnosed with Alzheimer's, no effective treatment exists. It's not for lack of trying. In the past three decades, over 200 Alzheimer's drug candidates have failed in human clinical trials.

RIGHT: MAGNIFIED VIEW OF SENESCENT CELLS. LEFT: SOURCES OF QUERCITIN — WHICH MAY HAVE ANTI-AGING PROPERTIES.



NEUROSCIENTIST KRISTIN BALDWIN. PHOTO BY JOELLE WIGGINS.

Cells from 'Wellderly' 90-plus -year-olds may help scientists understand how these 'super seniors' have maintained their health for so long.

One of the challenges is the limitations of existing research models for Alzheimer's, says Kristin Baldwin, Ph.D., a professor at the Dorris Neuroscience Center within TSRI's Department of Neuroscience in La Jolla.

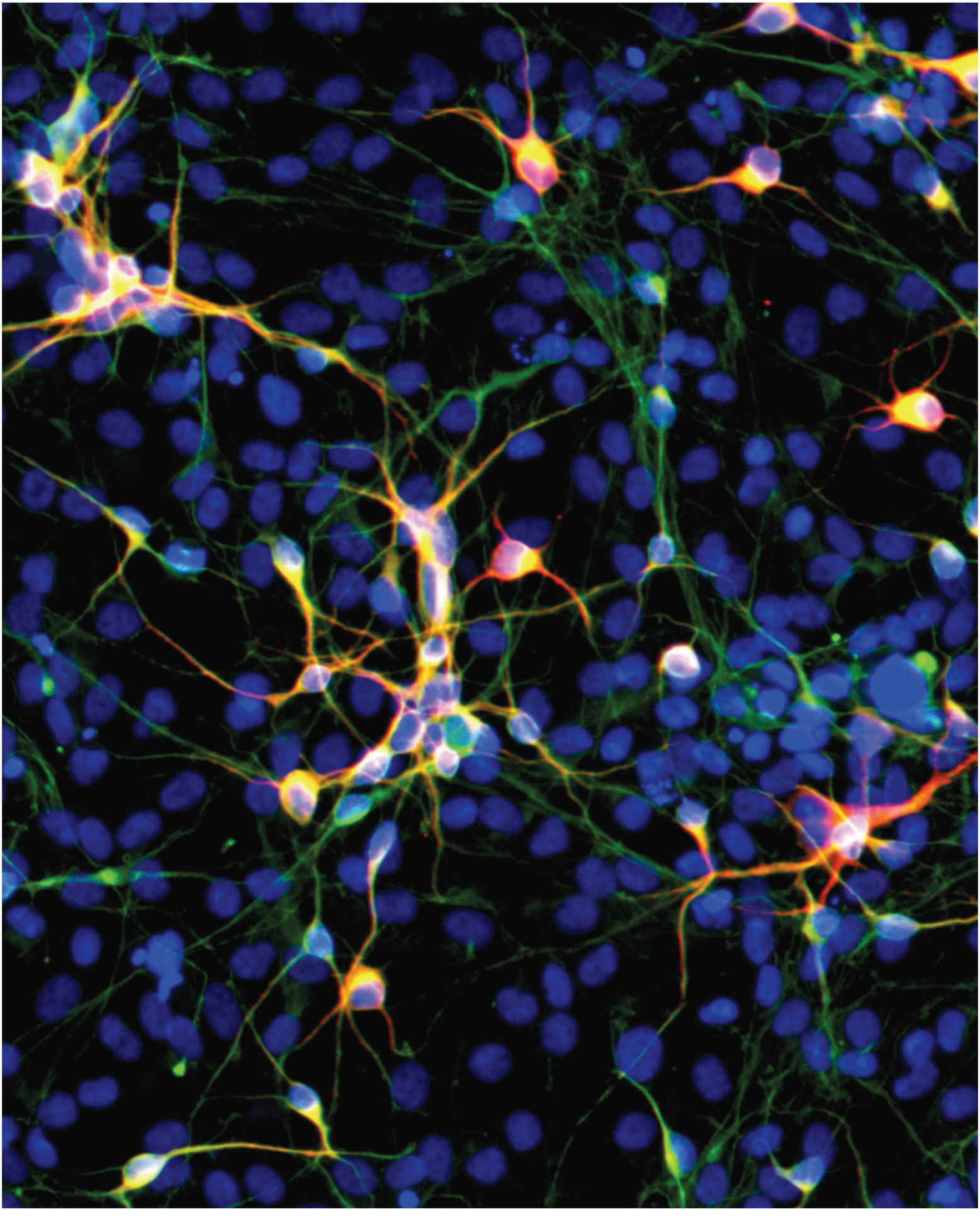
Baldwin explains that neurodegenerative diseases such as Alzheimer's only affect mature cells. Ideally, scientists would use mature cells for research, but when they attempt to produce model neurons from patient cells using stem cells, many of the signs of aging become reversed — the cells resemble those of newborns, which normally don't suffer aging diseases. Another problem is that the types of human neurons that can be made in a dish may not resemble the exact types of brain cells affected by Alzheimer's. The Baldwin lab is developing new technologies to overcome these issues.

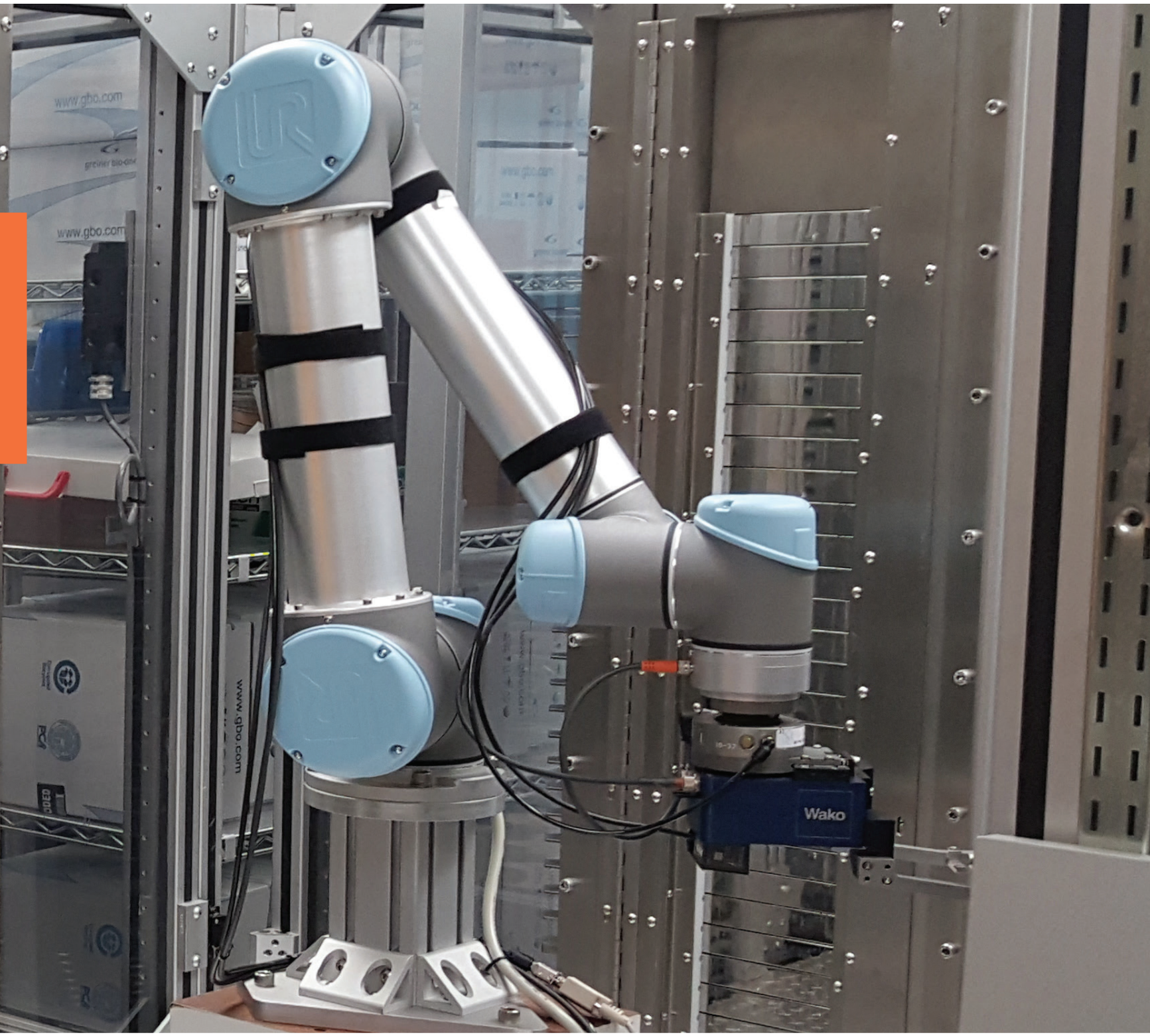
With a nod to the work of 2012 Nobel laureate Shinya Yamanaka, Ph.D., who showed how mature cells could be reprogrammed back to an early stem-cell state, Baldwin takes blood and skin cells from older donors and tests ways to convert them into useful research neurons, with the signatures of age. If she and her team succeed, the neurons made from patients with genetic predispositions to such diseases could be used to speed the development and lower the cost of potential new therapies.

Baldwin also collaborates with STSI Executive Director Eric Topol, M.D., on the study of healthy aging and cardiovascular disease. Topol's group has sequenced whole genomes and collected blood samples from a group of more than 1,400 exceptionally healthy super seniors — people he calls "wellderly," because they have lived into their 90s or even past 100 without having Alzheimer's disease or other chronic conditions.

Baldwin has reprogrammed the "wellderly" volunteers' cells into stem cells that resemble those of embryos. This may allow the scientists to understand how the seniors maintained their health for so long. The cells also could serve as valuable healthy comparison groups against cells from patients with cardiovascular diseases or neurodegeneration.

MAGNIFIED VIEW OF INDUCED NEURONS




www.gbo.com
Wako

Phenotypic screening is akin to studying thousands of novels by going straight to the final chapters, then zeroing in on the books with the best endings.

Nearby, at Calibr, biologist Kristen Johnson, Ph.D., is working with Peter Schultz, Ph.D., chief executive officer of TSRI and Calibr, to develop faster, more accurate research methods for studying aging-related diseases and potential treatments. They've become global leaders in the use of a large-scale high-throughput research technique called "phenotypic screening."

It's akin to studying thousands of novels by going straight to their final chapters, then zeroing in on the few books with the best ending. On finding them, the scientists go back to see how the stories actually unfolded, molecule by molecule, protein by protein, gene by gene.

Phenotypic screens have already led to development of a potential arthritis drug that is headed to a Phase I clinical trial. The drug is intended to jump-start the body's own dormant stem-cell cartilage-repair machinery.

Where is all this research work heading? The ideal would be to harness those "wellderly" traits in pursuit of a concept called "compression of morbidity," the maintenance of good health right up until the end of life, Niedernhofer says.

If research efforts to turn such discoveries into medications succeed, Niedernhofer envisions a future in which those of us with age-related conditions will head to a clinic a few times a year for our personalized, senescent-cell-clearing drug mix. Though we might lack the protective genome of the "wellderly" — thanks to their contributions to science, we could use medications to replicate their genomic good fortune.

Other approaches, including interventions to kick-start self-healing, may reach the market sooner, Johnson says, as innovative discoveries move into clinical trials.

Will improved healthspan lead to extended lifespan? That's a tougher question to answer.

Though the discoveries may not translate to super-centenarian lifespans like Calment's and Gotho's, Niedernhofer expresses optimism that they may one day enable extension of quality of life, without major illness or disability, for many people.

"We're going to have to be creative about this," she says. "We're running out of time."

ABOVE: CALIBR BIOLOGIST KRISTEN JOHNSON. PHOTO BY JOHN DOLE.
LEFT: CALIBR'S HIGH-THROUGHPUT SCREENING CAPABILITIES AND INFORMATICS TOOLS ARE CENTRAL TO DRUG DISCOVERY AND OPTIMIZATION EFFORTS.

JEFFERY KELLY, CO-CHAIR, DEPARTMENT OF MOLECULAR MEDICINE, AND LITA ANNENBERG HAZEN PROFESSOR OF CHEMISTRY AT TSRI.

Success Against Rare Disease Drives Hope for Alzheimer's Research

Alzheimer's disease piles loss upon loss. First there are the inconveniences. Words and familiar objects like keys and sunglasses elude. But then routes to known destinations like the grocery store become unfamiliar, confusing. Over time, the ability to manage financial and personal affairs erodes. Later, even the ability to recognize loved ones fades. An estimated 5.5 million people in the United States live with this progressive disease.

Losses within the Alzheimer's-affected brain mirror outward ones, beginning sight-unseen many years prior to symptoms. The brain's gray matter, the folded cortex, which processes thought, speech, sensory perception and decision-making, bears the brunt of the loss.

In the Alzheimer's-affected brain, the machinery of protein maintenance goes awry within neurons, and key proteins tangle like knotted yarn. Outside the brain cells, the cortex slowly accumulates sticky plaques made of a collection of misshapen and cut-off proteins, the most abundant one called beta amyloid. As Alzheimer's advances, the neurons' synapses, thread-like linkages where communications pass, gradually shrink and disappear, breaking circuits of experience and memory. The neurons themselves eventually die.

More than a century after Dr. Alois Alzheimer first described the brain of a patient who had died following memory loss and paranoia, much has been learned about the disease now bearing his name. Yet for all of the discoveries, and decades of focus on how to clear the plaques, the medical community still lacks an effective treatment. A debate rages within scientific circles about whether the plaques cause the death of neurons, a theory known as the "amyloid hypothesis," or whether the plaques are an observable side-effect of the disease-causing events.

At TSRI in La Jolla, the precise nature and conformation of the plaques and tangles occupies the brain of Jeffery Kelly, Ph.D., Co-Chair of the Department of Molecular Medicine, and the Lita Annenberg Hazen Professor of Chemistry within the Skaggs Institute for Chemical Biology.

At the molecular level, Kelly explains, proteins must hold a proper shape to perform their jobs in the body. The proteins that comprise the plaques, especially beta amyloid, are cut off at the wrong spot, and are misshapen or misfolded, becoming metabolic trash. Hundreds of clinical trials have tested therapies designed to take out the trash. But while the pharmaceutical industry has succeeded at clearing some forms of beta amyloid, the neurons themselves apparently continue to die, Kelly notes. The patients don't get better.

"The truth is, we don't know which aggregate structures, of many formed in patients, are causing the neuronal death," he says.

What Kelly now finds encouraging is the success he and others have had developing treatments for diseases similar to Alzheimer's, ones that also feature accumulation of misshapen proteins.

In a disease called hereditary transthyretin amyloidosis, genetic mutations enable transthyretin to become misshapen, leading to a progressive buildup of amyloid clumps in organs such as the heart, the gastrointestinal tract, peripheral nerves and the brain. Working at a molecular level, Kelly devised a drug that stabilizes the shape of the correctly folded protein so that it is incapable of forming the misshapen amyloid and, importantly, all other misshapen aggregate structures. The drug, tafamidis, has shown the ability to not only stop newly synthesized transthyretin from becoming misshapen, it slows progression of the disease itself in most patients, and goes a step further, improving neurological functioning in some patients.

Tafamidis represents a first among new drugs — a structure-based molecule that prevents a protein from taking on a toxic shape, in the process, slowing the progression of neurodegeneration. "This strategy of stabilizing the correctly folded form of a protein has been more successful than even I ever predicted," Kelly says.

That success suggests to him that the tactic of preventing disease progression by halting assembly of key misfolded proteins, as opposed to simply clearing them, remains an important path to explore in the fight against Alzheimer's, he says, because we do not know the exact misshapen proteins causing neuronal dysfunction and loss.

"In my world, the amyloid hypothesis, which states that the process of misshapen proteins aggregating leads to pathology, is likely correct," Kelly says. "However, the focus on clearing one aggregate type, amyloid, late in the course of Alzheimer's disease is risky. It would be better to stop all aggregates, both inside the cell and outside the cell, from forming early in the course of Alzheimer's disease."

In Appreciation of Visionary Donors

Scientific breakthroughs take time and sustained commitment — not only from scientists, but from the benefactors who enable that research through their selfless gifts.

Last summer, the U.S. Food and Drug Administration granted fast-track status to tafamidis, a drug discovered by Jeffery W. Kelly, Ph.D., the co-chair of TSRI's Department of Molecular Medicine. Tafamidis, designed to treat a heartbreaking, rare disease called transthyretin-related hereditary amyloidosis, has now been approved in 37 countries world-wide. The disease first presents as cardiomyopathy, a thickening of the heart muscle, or as damage to peripheral nerves in the hands and feet. As it advances, it causes progressive organ failure and untimely death. Until recently, there was no treatment, much less a cure, for children born with this genetic disease. Kelly's drug dramatically slows the progression, giving sufferers new hope. Tafamidis developed out of more than three decades of painstaking work studying protein structure and folding. Achievements like this cannot happen without support from dedicated partners like those featured on these pages.

In this edition of *Endeavor*, we recognize and thank the visionary donors whose unwavering commitment to TSRI science and education has continued through the years, making such discoveries possible. On the following pages you will meet donors who have given to TSRI in California over the past five years and to TSRI in Florida since its launch. Your gifts help TSRI fulfill its mission of serving humanity through expansion of basic biomedical science, improvement of health care, and advancement of science education. The steadfastness of your support is a source of inspiration.

Thank you.

The Dembling Endowment

A GIFT TO EASE PAIN AND DEPRESSION

The Dembling Endowment Fund for Drug Discovery and Human Health Research honors the memory of Donna Stacy Dembling, the daughter of consumer advocate Florence Dembling and the late Paul G. Dembling, Esq., co-author of the National Aeronautics and Space Act of 1958.

Donna Dembling valiantly battled major depressive disorder as a youth. "Had she lived past her 20s, Donna would surely have dedicated her career to easing the suffering of others," Florence Dembling said. "Even though she didn't enjoy a long life, she was always eager to help others. She was my cherished daughter who could feel everyone and everything's pain."

An estimated 16.1 million adults in the United States suffered at least one major depressive episode in the previous year, a number that represents 6.7 percent of all U.S. adults.

Florence Dembling and her late husband of 62 years supported the advancement of public awareness and advocacy for science throughout their lives. The Dembling gift has enabled Laura Bohn, Ph.D., professor in the departments of Molecular Medicine and Neuroscience at TSRI in Florida, to explore innovative strategies for alleviating pain, and to search for new approaches to fighting depression and addiction.

"Tremendous courage, vision and creativity are necessary to create something where there is no precedent," Florence Dembling said. "I encourage Dr. Bohn and researchers at Scripps to be bold, to go where no others have gone. Paraphrasing Neil Armstrong, let's take 'one giant leap for mankind' and discover a solution."

Bohn says the endowment gift of $1.625 million has enabled her to advance development of potential drugs that act on opioid receptors and enhance pain relief with diminished off-target side-effects. Bohn also investigates the cannabinoid receptors as possible therapeutic targets for enhanced pain control and mood.

"We are grateful to Mrs. Dembling — not only for her incredible generosity, but also for her deep appreciation for scientific discovery," Bohn said. "The Dembling Endowment has been instrumental in allowing us to be more creative and to move faster toward the realization of new medicines."

> "Tremendous courage, vision and creativity are necessary to create something where there is no precedent."
>
> — FLORENCE DEMBLING

$5M +
Anonymous
Harold L. Dorris Neuroscience Foundation
Samuel Yin

$1M - $5M
Anonymous
Alafi Family Foundation
The ALSAM Foundation
Patsy and George Conrades
Florence B. Dembling
Lawrence and Florence DeGeorge† Charitable Trust
The Richard and Helen DeVos Foundation
Mr. and Mrs. Alexander** W. Dreyfoos
George T. and Wilma A.† Elmore
Elizabeth Fago Smith
Celia Lipton Farris and
Victor W. Farris Foundation, Inc.
Marjorie Fink**
Frenchman's Creek Women For Cancer Research
Phillip** and Patricia Frost
The William R. Kenan, Jr. Charitable Trust
Norma and Leonard Klorfine
Margaret Q. Landenberger Foundation
Nancy Lurie Marks Family Foundation
John Jay Moores
Esther B. O'Keeffe Foundation
Paul and Cleo Schimmel

$500K - $999K
Anonymous (2)
Anonymous Faculty
BallenIsles Mens Golf Association
The Donald E. and Delia B. Baxter Foundation
John* and Susan Diekman
Olivia and Peter* Farrell
Estate of Allan and Beverly Gale
Arnold† and Arlene Goldstein
Estate of Charles E. Henningsen
Josilyn's Faith Foundation for Prader Willi Syndrome
Jeffrey W. Kelly, Ph.D.
Estate of W. Keith Kellogg II and Janet R. Kellogg
Iris and Junming Le Foundation
Becky and Jimmy Mayer
Medical Research Charities
Office Depot
PGA National: Cancer Research Initiatives
Dr. and Mrs. Ed Roberts
Dr. and Mrs. Zaverio M. Ruggeri
Drs. Pete and Jocelyn Schultz
Shaffer Family Foundation
Estate of Lesly Starr Shelton
Dr. and Mrs. Chi-Huey Wong

Ellen Browning Scripps Foundation

Ellen Browning Scripps shaped the landscape of San Diego with her generous giving and commitment to education, science, community outreach and the arts. Ellen Browning Scripps was born in 1836 to a working-class Detroit family. She amassed her independent fortune through investment in her brothers' penny press business, which evolved into a newspaper empire with national circulation. She moved to San Diego in the late 1890s and fell in love with the laid-back lifestyle and warm climate. She had a keen interest in science and biology and founded the Scripps Institution of Oceanography in 1905. She went on to "invest" (as she liked to call it) in Scripps Hospital, Scripps Clinic, the La Jolla Woman's Club, the La Jolla Library, and what is now The Scripps Research Institute. She was a straightforward, humble person who believed that "the most important and beautiful gift one human being can give to another is, in some way, to make life a little better to live." The Ellen Browning Scripps Foundation was established by her nephew, Robert Scripps, following her death in 1932 and currently supports several TSRI researchers in various fields.

$250K - $499K

Anonymous
The Saul and Theresa Esman Foundation, Inc.
Fidelity Charitable Gift Fund
Lottie French Lewis Fund
Amin J.** and Julie Khoury
Barbara and Herbert† Mines
Mission Edge San Diego
Estate of Everett Nussman
Optimer Pharmaceuticals, Inc.
The Rainwater Charitable Foundation
The Rendina Family Foundation
The San Diego Foundation
Estate of Rona Elise Selbst
Estate of Thomas L. Shepherd
Carol Vassiliadis
Michael and Alice Volechenisky†
RJ Foundation
Barbara and Herbert Shear

$100K - $249K

American Federation For Aging Research
Amgen, Inc.
Lita Annenberg Hazen Charitable Trust
ARCS® Foundation, Inc.
The Cornelia T. Bailey Foundation
Mr. Albert Berger and Ms. Carol Auerbach
Elise M. Besthoff Charitable Foundation
Bristol-Myers Squibb Company
Peter and Janice Brock

$100K - $249K CONT'D

Bruce and Anne Bundy Foundation
J. Gary** and Dawn Burkhead
Ronald W. Burkle Foundation
California Community Foundation
Ollie Jo Cole
Combined Jewish Philanthropies
Community Foundation for
Palm Beach and Martin Counties
The Ray Thomas Edwards Foundation
Abraham and Rose Ellis Foundation
Paul Emple
Joan R. Fisher
Samuel J. and Connie M. Frankino
Charitable Foundation
Estate of Stanley H. Gist
Eugenia C. Glow
Estate of Helen H. Guyan
Susan and Gerald L. Holm
Dr. Paul A. Hurwitz Fund For Cardiovascular Research
Infinity Clean Air Development Pte. Ltd.
Janney Montgomery Scott LLC
Jewish Community Foundation
Leonard and Jane Korman
Dr. Stuart and Lisa Lipton
Gilbert J. Martin Foundation
Estate of Walter and Eleanor Malen

Celia Lipton Farris and Victor W. Farris Foundation

In 2016, The Celia Lipton Farris and Victor W. Farris Foundation made a $1.135 million gift to The Scripps Research Institute (TSRI) to create the Farris Foundation Endowed Graduate Fellowship on the Jupiter, Florida campus. The new Farris Foundation Endowed Graduate Fellowship will provide annual support for doctoral students at Scripps Florida in perpetuity. "Our gift is an investment in the continued strength of biomedical research at Scripps Florida," said Christine Koehn, executive director of the Farris Foundation, "so that young scholars will be able to reach their full potential as world-class scientists." The Foundation, created in 1986 by a merger of the Victor W. Farris Foundation and the Celia Lipton Farris Foundation, seeks to support projects that provide the structure, encouragement and incentive that enable people to help themselves lead more successful, inspired and fulfilling lives.

$100K - $249K CONT'D

Gladys and John McCubbin
Samuel C†. and Joyce McLendon
Denise and William A. Meyer
The David Minkin Foundation
National Western Life Insurance Company
Parkinson's Association of San Diego
Mark Pearson*
Paul & Janice B. Plotkin Family Foundation
PNC Bank
PNC Wealth Management
The Marni and Morris Propp Family Foundation
Estate of Henry and Barbara Reed
Edward Ricci and Mary Lupo
Mr. James L. Robo and Ms. Meredith Trim
Stephen M. and Toni† Rosenberg
Linda Sandelman
Ellen Browning Scripps Foundation
Scripps Health Movement Disorder & Parkinson's Disease Clinic
Fred Sieber
Carolyn and A. Richard Sloane
Leslie and Richard Stone
Estate of Rhoda Karin Turley
Vanguard Charitable Endowment Program
VWR Charitable Foundation
Mimi and Frank Walsh
Dr. Charles and Mrs. Juliette Weissmann

$50K - $99,999K

Agency for Science, Technology and Research
American Chemical Society
American Fundraising Auctions, Inc.
Marc R. Azar
Margaret Bilotti
Elise M. Besthoff Charitable Foundation
BMO Harris Bank
The Honorable Ann Brown and Don Brown
Buck Family Foundation
Catalyst Real Estate Group, Inc.
Children's Healthcare Charity, Inc.
Andrew and Violet Cianciotto
Hannah S. & Samuel A. Cohn Memorial Foundation
Collette Family Trust
The John and Jordan Davis Foundation
Ann and Thomas E.** Dewey
Helen T. Farschon
Florida State Auxiliary - Fraternal Order of Eagles
Fraternal Order of Eagles, Aerie No. 4267
Alan and Susan Fuirst
Genentech Foundation
Jane and Richard** Gephardt
Judy and John Goodman, MD
Estate of Peggy Hadley
Irene M. Hanson
Nancy and Joel Hart
Estate of Virginia G. Kahse
Estate of Robert W. Kerney

The Donald E. and Delia Baxter Foundation

In 1959, Delia Baxter created the Donald E. Baxter Foundation in memory of her husband, a prominent American engineer, physician and scientist. During World War I, the Rockefeller Foundation sent Dr. Baxter to China to oversee construction of the new Peking University Medical School. While on assignment, he observed a startling number of patient deaths due to simple dehydration. Once back in the States, Dr. Baxter designed and patented a revolutionary way to consistently administer fluids to sick patients: by using pouches that dispense necessary liquids intravenously. His invention and subsequent medical supply company, Don Baxter Inc., became incredibly successful. Baxter's wife, Delia, was a nurse and took charge of the company upon Dr. Baxter's death in 1935. Today, Don Baxter Inc. is part of Baxter International. Delia passed away in 1982 and the foundation was renamed The Donald E. and Delia Baxter foundation in her honor. The foundation's main goal is the advancement of STEM education and scientific research, primarily at schools of higher education in California.

$50K - $99,999K CONT'D

Hazen Polsky Foundation
Julie Hill
A.C. Israel Foundation, Inc.
Edward & Bethel Kean Charitable Foundation
Leanna Landsmann and Milton J. Block
George W. and Carol A. Lattimer
Peter A. Levine
Lilly USA LLC
James L. Long
Agnes and Alan** Mendelson
Millipore
Miramar Fiduciary Corporation
Morgan Stanley Global Impact Funding Trust, Inc.
Marilyn and Jay Nelson
Novartis
Geri Orta
Prostate Cancer Foundation
Quantum Foundation
Fredric and Lundy Reynolds Family Foundation
Robert P. Scripps, Sr.†
Anne and Jeffrey Stanfield
Estate of Victor S. Sauer
Think Pink Foundation
Amy and Horacio** Valeiras
Peter K. Vogt. Ph.D.
Warren Family Foundation
The Weiler Foundation, Inc.
Western National Life Insurance Company
Jill and Harold Wilkinson III

$25K - $49,999K

Anonymous (3)
The Abrams Charitable Trust
Allstate Life Insurance Company
Sharon and Carlos Arbelaez
Kathy and Michael Azeez
BallenIsles Charities Foundation, Inc.
Bank of America
Sadrudin H. Bharwani
The Biogen Idec Foundation
The Walter and Adi Blum Foundation
Jeanette Buckley
Kevin G. Craven
Fred Craves Foundation
Emory University
Dennis Fenton
Florida Power & Light
Fraternal Order of Eagles, Aerie No. 4267
Tess Gerritsen
Gilead Sciences
Robert M. Golden Foundation
Alicia Hallett
William A. Haseltine Charitable Foundation

$25K - $49,999K CONT'D

Terry G. Hazard
Hogan Foundation
Robert and Margaret Hulter
Thomas H. Insley
Institute of Chemical and Engineering Sciences
June Jones
Edward Kamolz
Las Patronas
Ira and Renee Levine
Lydian Bank & Trust
Yongrui Ma
The Menard Family Foundation
Irene Miller
Neuronetrix Solutions, LLC
The Kenneth T. and Eileen L. Norris Foundation
Northern Trust Bank of Florida N.A.
Beverly and James Paulson
Quantum Foundation
Rolling Ridge Ranch
Estate of John A. and Marjorie B. Sage
Edward (Sandy) J. Sanderson**
Mr. and Mrs. Sandford Smith
Professor and Mrs. K. Barry Sharpless
David E. Shaw
Charles Spear Charitable Trust
Ruth Stein
Estate of Richard E. Stern
UBS Financial Services Inc.
Ullmann Family Foundation
The Unforgettable Fund, Inc.
United States Medical Supply
Jocelyn and Richard H. Vortmann
Xueqian Wang
Del E. Webb Foundation
Hongmin Zhao

Asterisks (*) indicate trustees.
Double asterisks (**) indicate trustee emeritus.
Daggers (†) indicate deceased.

This issue of Endeavor highlights donors to TSRI Florida since its inception and donors to TSRI California since 2012.

For more information contact us at (858) 784-2339 or philanthropy@scripps.edu

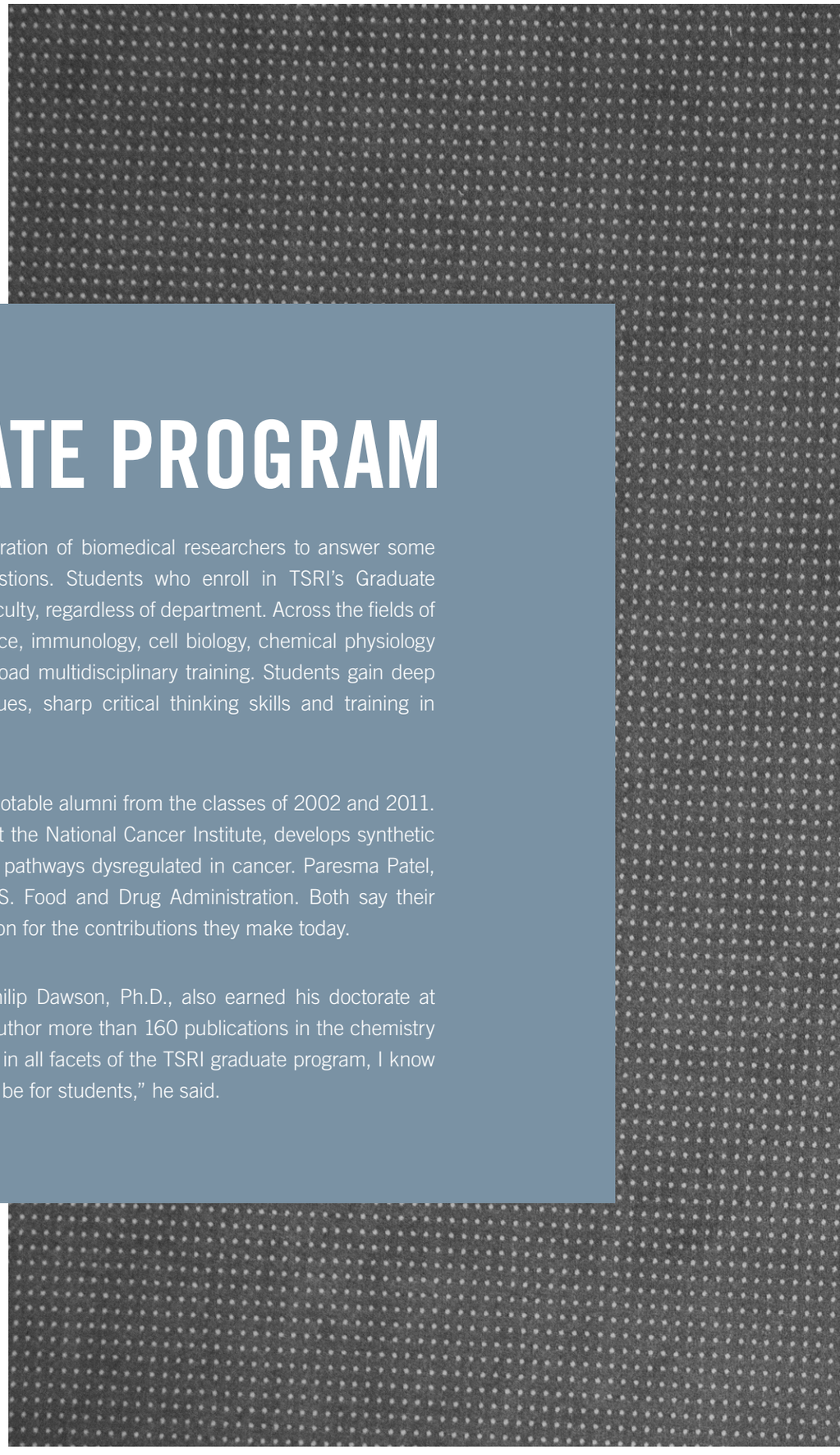
Thank you, Scripps Research Development Staff

TSRI GRADUATE PROGRAM

For 25 years, TSRI has prepared the next generation of biomedical researchers to answer some of the world's most challenging scientific questions. Students who enroll in TSRI's Graduate Program gain access to its entire distinguished faculty, regardless of department. Across the fields of chemistry, chemical biology, biology, neuroscience, immunology, cell biology, chemical physiology and biophysics, the Graduate Program offers broad multidisciplinary training. Students gain deep scientific knowledge, expert laboratory techniques, sharp critical thinking skills and training in effective communication.

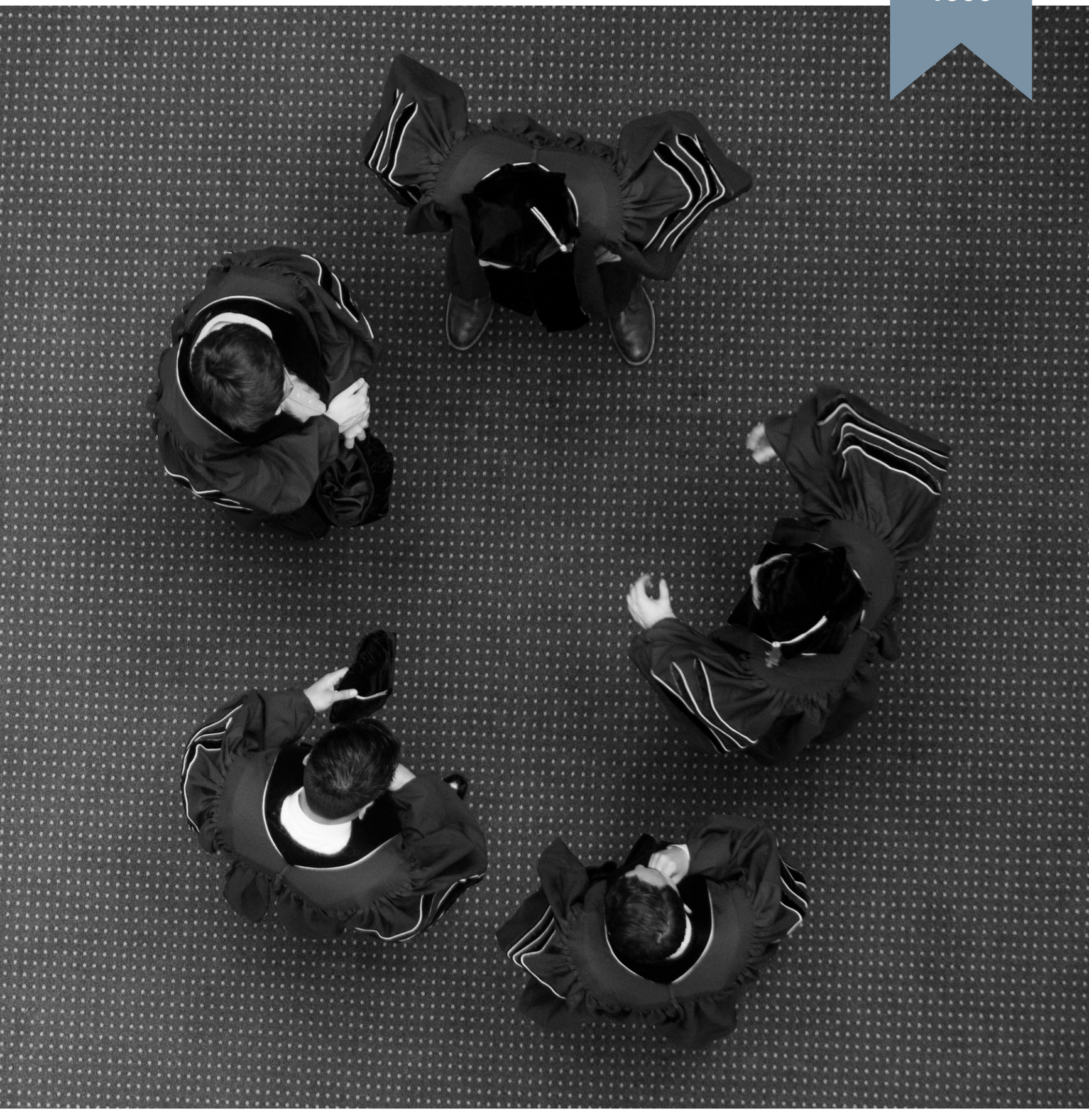
On the following pages, you will read about two notable alumni from the classes of 2002 and 2011. Federico Bernal, Ph.D., a principal investigator at the National Cancer Institute, develops synthetic molecules to probe, and potentially fix, signaling pathways dysregulated in cancer. Paresma Patel, Ph.D. reviews new drug applications for the U.S. Food and Drug Administration. Both say their experience at TSRI provided invaluable preparation for the contributions they make today.

The new dean of TSRI's Graduate Program, Philip Dawson, Ph.D., also earned his doctorate at Scripps Research, in 1996. He has gone on to author more than 160 publications in the chemistry of proteins. "As someone who has been involved in all facets of the TSRI graduate program, I know exactly how transformational this experience can be for students," he said.



LOCATIONS: LA JOLLA, CALIFORNIA + JUPITER, FLORIDA

FOUNDED
1989



CURRENT STUDENTS: 300+ **FACULTY AND STAFF:** 171 **POSTDOCTORAL FELLOWS:** 520 **ALUMNI:** 700+ **WWW:** EDUCATION.SCRIPPS.EDU

FEDERICO BERNAL STUDIED SYNTHETIC CHEMISTRY WHILE AT TSRI.

Thanks to chance — and Bernal's TSRI education — a new cancer therapy is in clinical trials.

Leaving Nothing to Chance in the Fight Against Cancer

NCI RESEARCHER AND TSRI ALUMNUS FEDERICO BERNAL, PH.D.

Along life's journey, people often speak of serendipity, where something very good happens by accident or chance rather than by design. That term seems apt to describe several incidents in the life of Federico Bernal, Ph.D., an alumnus of The Scripps Research Institute's Graduate Program, who is now an investigator at the National Cancer Institute.

Thanks to fortuitous chance — and Bernal's stellar education at TSRI in the early 2000s — a new cancer therapy is in clinical trials. A novel treatment for a frequent complication of cystic fibrosis is also moving forward.

In 2000, when Bernal arrived in San Diego to interview for a spot in TSRI's Graduate Program, a young graduate student, Chris Boddy, greeted him at the airport.

"Chris Boddy was the first student I met from Scripps Research," recalled Bernal. The two were destined to become good friends as graduate students in the lab of famed chemist K.C. Nicolaou. In Nicolaou's lab, they learned to synthesize complex compounds on a large scale, rapidly and efficiently. That high-level skill, coupled with their friendship, would ultimately lead to their fruitful collaboration.

After graduation their paths crossed again at a research conference a few years later, and they discussed collaborating on the development of antibacterial compounds.

From that effort grew their novel work toward stopping *Pseudomonas aeruginosa*, the bane of cystic fibrosis patients. "It creeps into the crevices of the respiratory tract, where it produces chronic lung infections that end up being lethal to many cystic fibrosis patients," explained Bernal.

Bernal and Boddy, now a professor at the University of Ottawa in Canada, designed compounds that block activation of a protein necessary for the bacteria's survival. Their proof of principle study has shown good results against *E. coli*, a simpler organism. The next step is testing their hypothesis in pathogenic bacteria, for which they've been offered assistance by the U.S. Army Medical Research Institute of Infectious Diseases.

"They're helping us test our compounds against some very lethal pathogens," he said, noting their approach may ultimately prove useful against numerous bacteria.

Fresh off of receiving his doctorate at TSRI in 2002, Bernal found himself in a Harvard lab taking on the unpopular task of synthesizing specialized compounds known as stapled peptides.

"The other postdocs thought it was way too complicated and didn't want to touch it with a 10-foot pole," said Bernal of his postdoctoral days at Harvard. "But it was second nature to me because of my training in Nicolaou's lab."

That early effort led Bernal to focus his research on stapled peptides. Incorporating "staples" of hydrocarbons to peptides with therapeutic potential can improve their selectivity, reducing undesired side-effects. Today, a cancer treatment based on a stapled peptide is being tested in Phase 2 clinical trials. The treatment targets solid tumors in certain cancers, primarily lymphoma and melanoma. Most notably, it has shown promise in treating melanoma's most advanced stages.

Bernal is continuing his cancer research as a principal investigator at the National Cancer Institute, part of the National Institutes of Health. He joined NCI in 2010 after completing his postdoctoral studies at Harvard and spending three years at the Dana Farber Cancer Institute.

At NCI, Bernal uses synthetic molecules to probe, and potentially fix, signaling pathways dysregulated in cancer. "Our focus (as cancer researchers) needs to be on developing more targeted cancer treatments with less collateral damage to healthy tissues," he said. "Even though we have treatments, such as chemotherapy and radiation, some of their side effects can be very serious."

"That's where the power of chemistry comes in," continued Bernal, recalling his early TSRI training in that area. "Knowing how to make stuff and change compounds will enable us to fine-tune our discoveries, so we can develop new therapies that avoid these problems."

by

BONNIE WARD

PARESMA PATEL WORKS WITH DRUG APPLICANTS AT THE FDA.

Enabling Access to New Lifesaving Therapies

FDA REVIEWER AND TSRI ALUMNA PARESMA PATEL, PH.D.

Eighteen years ago, while a teenager in high school, Paresma "Pinky" Patel, Ph.D., received a shocking education about the importance of medical science.

"My father was in a car accident and received a spinal cord injury," said Patel, a 2011 graduate of The Scripps Research Institutes's Graduate Program. The incident left her father paraplegic. "That experience makes you think about human health and what the scientific community can offer," she said.

Patel believes that's one of the reasons her career took her to the U.S. Food and Drug Administration (FDA), where she's part of a multi-disciplinary team reviewing applications for new therapies. "I enjoy working in the public sector," she said. "It is patient-driven, and really about the public good."

Patel credits her TSRI training for providing the solid science background needed to serve as an FDA chemistry reviewer. She analyzes the complex data submitted to the chemistry, manufacturing and controls sections, and works with drug applicants before and during clinical trials. After all of the data are submitted, she participates in the drug's final approval process.

At TSRI, she studied organic chemistry in the lab of Dale Boger, Ph.D., an internationally recognized medicinal and organic chemist who co-chairs TSRI's Department of Chemistry, holding the Richard and Alice Cramer Professor of Chemistry endowed chair, and an appointment with the Skaggs Institute for Chemical Biology. In recent years, Boger's lab has been

Patel's TSRI training provided the science background needed to serve as an FDA chemistry reviewer.

widely praised for discovering ways to dramatically improve the potency of a major anti-cancer drug, vinblastine, as well as the life-saving antibiotic vancomycin. Both feats were possible through rational molecular modifications enabled by organic chemistry.

"We learned about new ways to discover drugs, how to modify natural products to make them more efficacious and many other skills that have been transferable to my career," said Patel of her time in the Boger Lab. "It gave me a very strong background in how to approach problems in medicinal chemistry and drug discovery."

Patel's interest in science started early in life, but she wasn't sure whether she wanted to be a doctor or a scientist. She earned a bachelor's degree in chemistry at the University of North Carolina at Chapel Hill, after which she worked for a time at a small pharmaceutical company. Unlike college, where she focused on basic chemistry, her work there had direct patient applications. "We were using organic chemistry to make compounds that were applicable to human health," she said. That drew her in and solidified her decision to go into research.

Patel was delighted when she was accepted into TSRI's Graduate Program in organic chemistry. "Scripps had a great reputation," she said. "One of the things I liked about the program was that it really had a research focus. It mixed both a strong chemistry and a strong biology program," she said.

Patel said that training has been very helpful as she reviews drugs in the oncology division. Since joining the FDA in 2015, she's been involved in the approval of a number of cancer drugs, including the breakthrough therapy Vyxeos, approved in August for acute myeloid leukemia.

One of the most enjoyable aspects of her position, said Patel, is collaborating with team members from different disciplines. But her favorite aspect is helping patients receive access to new therapies. "To me it's exciting to know that this is something that could really improve their lives."

by

BONNIE WARD

LAB NOTES

Faculty Profile: Pat Griffin

Patrick Griffin, Ph.D., was one of the first scientists to begin research at TSRI's Jupiter, Florida campus in 2004, before the institute even had a permanent physical campus. Griffin studies the structure and function of receptors throughout the body. His work has provided crucial insights into cancer, metabolism and autoimmune diseases. When Griffin isn't in the lab, he takes advantage of Jupiter's outdoor lifestyle by golfing, fishing, diving in the ocean with his eldest daughter, and cave diving in central Florida. *Endeavor* sat down with Griffin to learn how he approaches risk in cave diving and in research.

Q: Why did you decide to pursue a career in research?

My dad had a mechanical background and was very interested in geography. His fascination with earth science made me interested in all areas of science. I entered the engineering program at Syracuse University, but became more interested in physical and analytical chemistry. Problem was, there weren't many jobs at that time for someone at the bachelor's level, so one of my teaching assistants encouraged me to get a Ph.D. I followed his advice and enrolled in the University of Virginia. I was debating which lab to join when, during a night of faculty presentations, Professor Donald Hunt took the stage. He was known for being tough, but he had just returned from a sabbatical in the United Kingdom where he had observed the first analysis of an intact protein by mass spectrometry, and he was so excited and animated about what he had seen that I decided to join his lab.

It turned out to be a great decision, as Hunt was leading the charge on a new field that today is knowns as proteomics[1] — the study of the protein component of cells, which determines their structure and how they are altered and modified to carry out distinct functions in living organisms.

PAT GRIFFIN, CO-CHAIR OF THE DEPARTMENT OF MOLECULAR MEDICINE AT TSRI, SEEKS THE UNKNOWN, UNDER WATER AND IN HIS LAB.

by

EMMA YASINSKI

LEFT: GRIFFIN ON TSRI JUPITER CAMPUS. PHOTO BY LILA PHOTO. RIGHT: GRIFFIN OFTEN DIVES JUPITER INLET WITH HIS ELDEST DAUGHTER.

Q: After graduate school, you spent significant time doing research in industry. What brought you back to academia at TSRI?

Hugh Rosen, Ph.D., a faculty member at Scripps in La Jolla, and I were collaborators, colleagues and friends at Merck. When I made the decision to leave industry I emailed him and my phone rang a few minutes later. Hugh asked me if I had heard about Scripps Florida. I don't think Google existed then, so I typed "Scripps Florida" into Netscape and there was a single picture of Jeb Bush, then Governor of Florida, shaking hands with (former TSRI President) Richard Lerner, M.D. That was all the information that was available. At that time, there was nothing in place in Jupiter, but I knew enough people at Scripps La Jolla to take the chance. It was kind of like sky diving…I just jumped.

Q: What has kept you at TSRI for the past 13 years?

The campus was designed and built with the idea of merging chemistry, advanced technologies and biology to help facilitate and drive translational research. Since my research requires access to state-of-the-art technologies and medicinal chemists, Scripps Florida is a perfect place for my lab.

Q: What kind of long-term impact do you see for your academic research?

Our research is focused on finding new approaches for the treatment of metabolic diseases such as diabetes and obesity; for autoimmune disorders such as rheumatoid arthritis, and for cancer. Specifically, we are focusing on ways to enhance the body's immune response to tumors, and targeting transcription factors that impact pancreatic cancer. We have several examples where our publications revealed a protein target that was actually druggable using synthetic compounds — many pharmaceutical companies jumped on that information. Hopefully those efforts will lead to the development of new medicines that will have a positive impact on human health.

Q: What advice do you have for those just starting their scientific research careers?

I have to remind students not to rely on the output from all the sophisticated analytical instruments available today. You need to look at the raw data, the data the instrument actually generates. The raw data still is what it was during my early research years, we just had to sit

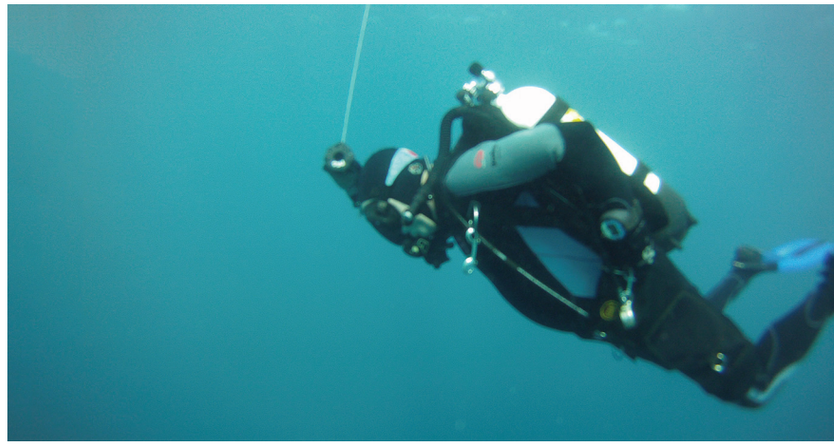
there and manually figure stuff out. That basic understanding is still important because there are unusual findings in these experiments and the software won't be able to answer those questions. The software relies on databases of known information. If it isn't in the database or contemplated as a modification, the software won't find it.

Q: How did you get started cave diving?

My eldest daughter was entering 10th grade when we moved from New Jersey to Florida. As one of the bribes, I said "as soon as we get there we'll learn how to scuba dive," because you can scuba dive right off the Jupiter Inlet which is less than 5 miles from Scripps Florida. Of course, I had never gone scuba diving. I get claustrophobic and I am susceptible to motion sickness just watching TV, so I was hoping that promise somehow would be forgotten — but she didn't. So shortly after settling in to life in Jupiter, we got our certification. And within a short period of time we had racked up a couple of hundred dives or so. My daughter went on to dive around the world in places like Fiji, the Red Sea and Baja.

Q: What is the greatest challenge to cave diving?

The most significant difference between cave diving and ocean diving is that if you have a problem in the ocean you can pop to the surface. In a cave, the only way to get to the surface is to go back out the way you came in. The cave systems in South Florida are huge; they run forever and it's easy to get lost. It takes incredible teamwork, particularly during the certification process, to master the technical and physiological aspects of cave diving. Inside the cave, the instructor comes up behind you and turns off your valves and you have to immediately work with your partner to share their air. Then we practice with the lights out. The cave is the darkest place you'll ever be. When the lights go off, you see nothing. Teamwork is everything, and the only way to overcome your fears.



Q: What lessons from cave diving can you carry back with you to the lab?

We kept going to the same cave over and over and over and tried to go a little further each time. We would not go deeper until we were completely confident we knew everything there was to know about that specific area of the cave and how to do that dive safely. If you do something in the lab and you get an answer that you're looking for, that's great. Regardless, you need to do it again and again to be confident. I don't trust anything 100 percent until I see it multiple times. It is really about skill, challenging yourself and teamwork. This is the only way to be successful in translational research. Working in isolation will never have the same impact as teamwork.

CAVE DIVING, LIKE SCIENCE REQUIRES TEAMWORK, GRIFFIN SAYS.

1. The term proteomics was coined in 1997 in analogy with genomics, the study of the genome.

If I have seen further,
it is by standing on
the shoulders of giants.

— SIR ISAAC NEWTON

Published by

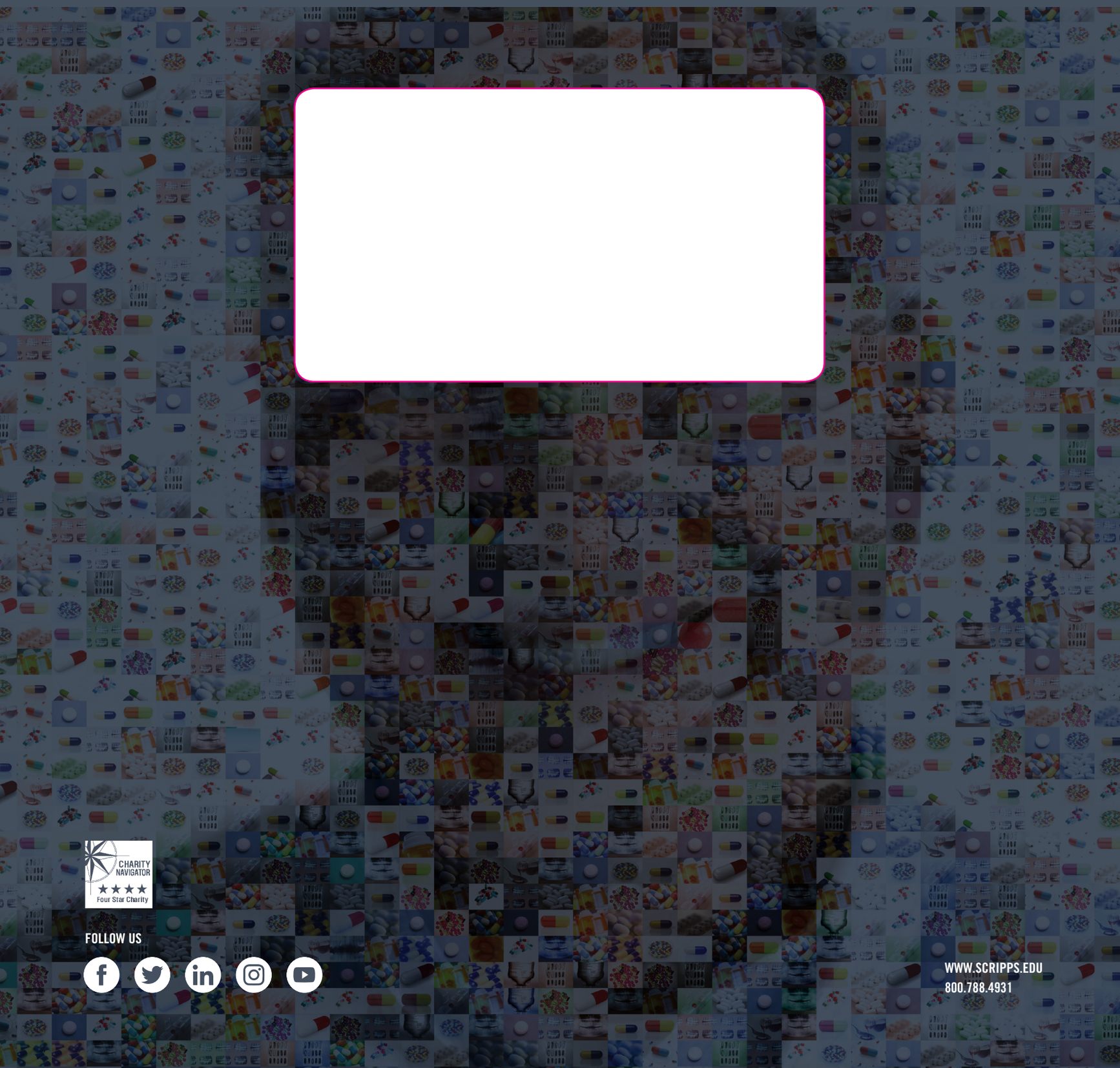
TSRI PRESS.

CONTRIBUTING WRITERS STACEY SINGER DELOYE, BONNIE WARD, EMMA YASINSKI **EDITOR** STACEY SINGER DELOYE **PHOTOGRAPHERS** PAUL BARNETT, FAITH HARK, JACQUELINE SHERMAN **DESIGN + PRODUCTION** JACQUELINE SHERMAN **PRINTING** NEYENESCH PRINTERS

TSRI LA JOLLA / 10550 NORTH TORREY PINES ROAD / LA JOLLA, CALIFORNIA 92037 TSRI FLORIDA / 130 SCRIPPS WAY / JUPITER, FLORIDA 33458

THE SCRIPPS RESEARCH INSTITUTE / OFFICE OF COMMUNICATIONS, TPC-8
10550 NORTH TORREY PINES ROAD / LA JOLLA, CALIFORNIA 92037

NON-PROFIT
ORGANIZATION
US POSTAGE
PAID
PERMIT NO 761
SAN DIEGO, CA



FOLLOW US

WWW.SCRIPPS.EDU
800.788.4931