endeavor

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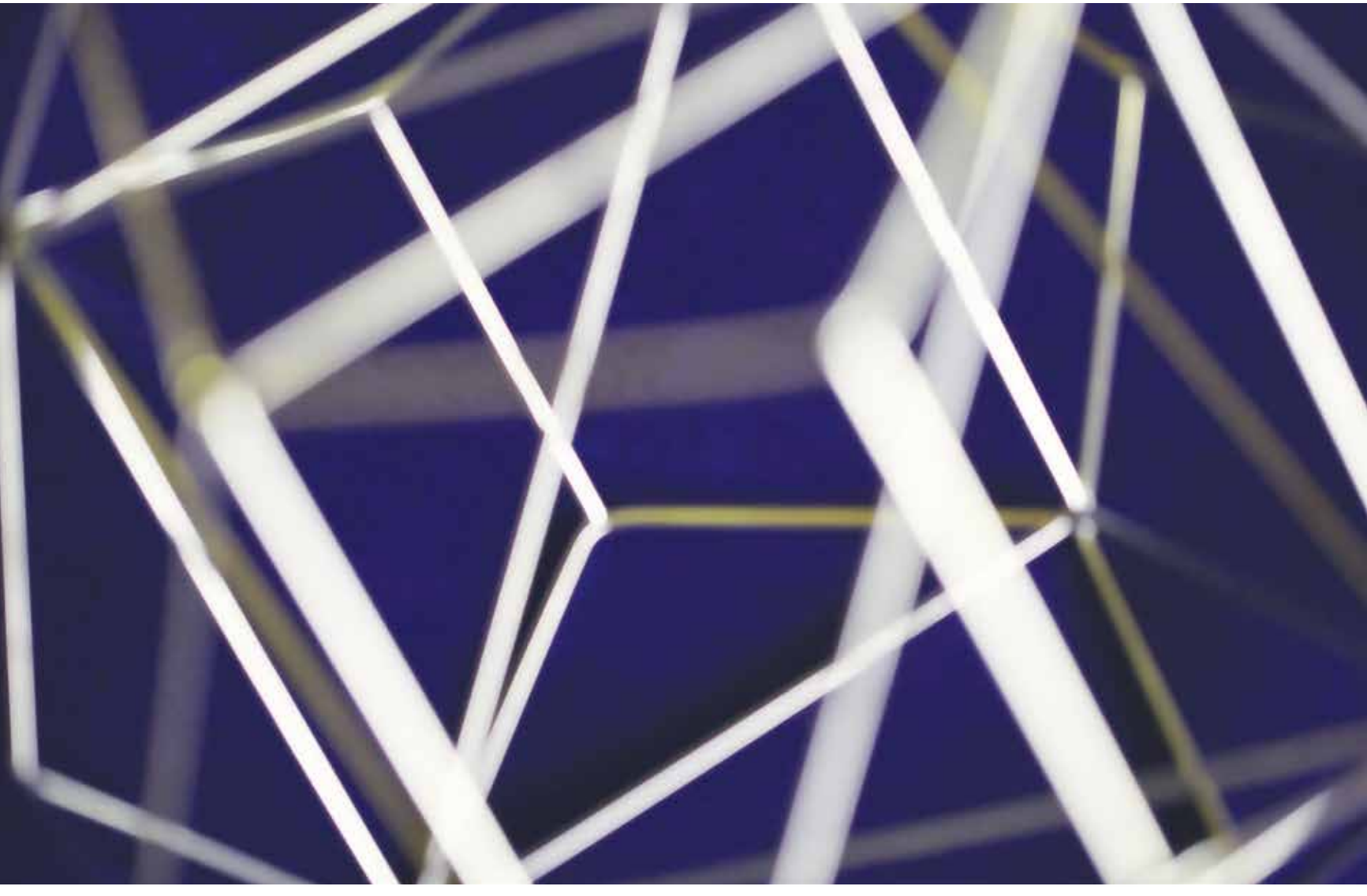

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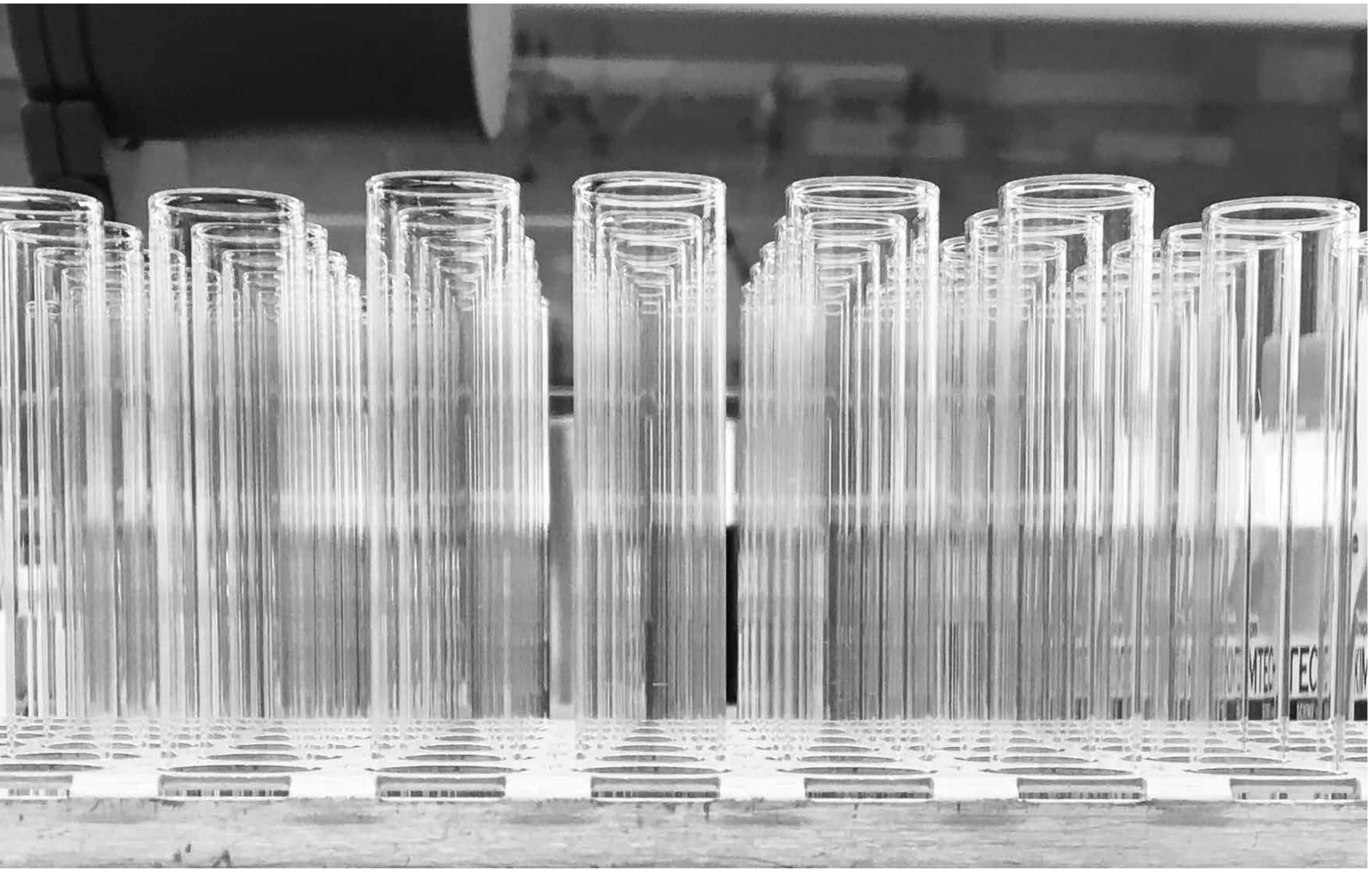


COVER IMAGE BY MAITE BENITO AGAHNIA, 2017. The cover image represents the idea of connectivity and collaboration through the intersection of lines. The lines are able to stand alone, but when joined with others, create a strong cohesive group, much like the interaction between TSRI and Calibr. The contrast between the light and dark, as well as the varied thickness and angles of the lines represent different areas of focus and strength. When intertwined, the lines create a new, stronger bond.

Letter from the President

Welcome to the first issue of the newly relaunched *Endeavor* — a quarterly vehicle for sharing important information about TSRI, our impressive faculty, their science, and the vision we believe will continue to drive the future growth and success of the Institute.

This is an exciting time at TSRI. In the last year alone, we have assembled a terrific new Board of Directors, created compelling five-year scientific and financial strategic plans for the Institute, and formed an alliance with one of the world's leading non-profit institutes in the field of translational research — the California Institute for Biomedical Research (Calibr) — all while continuing to push the boundaries of groundbreaking basic biomedical research.

Critical to TSRI's long-term vision is the alliance with Calibr, which integrates the Institute's outstanding basic scientific research with Calibr's translational research capabilities into a new bench-to-bedside model designed to accelerate the development of life-saving medicines. Read more about the inception of Calibr and the individuals who helped make it one of the most well-known translational research institutes in the world (page 16). You will also read about a unique new funding model designed to accelerate drug discovery efforts, while also creating a self-sustaining, evergreen funding source for ongoing research.

I also want to express our enthusiasm for the opportunity to work more closely with Scripps Translational Science Institute (STSI) Founder and Director Eric Topol, M.D., and the rest of the STSI team in their efforts to advance personalized medicine. Look for more information about the partnership between TSRI and STSI in a future issue of *Endeavor*.

Among the outstanding faculty members highlighted in this issue is Chemistry Professor Jin-Quan Yu, Ph.D., recipient of the 2016 MacArthur Fellowship or "genius" grant (page 6). He is the second TSRI chemist to receive recognition from the MacArthur Foundation. (TSRI Chemistry Professor Phil Baran, Ph.D., received the prize in 2013.) I would also encourage you to explore the Q&A with Nobuyoshi Suto, Ph.D., who, in addition to his role as TSRI assistant professor, neuroscience, is a jazz pianist and composer, with eight albums to his credit (page 58).

In addition to underscoring the impact of TSRI's world-renowned faculty, this issue also highlights the impact of our Top 10-ranked Graduate Program, which is celebrating its 25th Commencement Ceremony this month. Hear more from alumna Jovana Grbic, Ph.D., about how she is applying her scientific expertise in a very different career path (page 52).

Finally, given the growing global impact of Zika virus and its potential impact on babies exposed in utero, we wanted to share some of the critical research currently underway to better understand the virus and develop potential treatments and/or cures (page 28).

The most important aspect of this particular issue, however, is the opportunity to recognize and thank TSRI's generous donors. In challenging times, when funding from the federal government is uncertain, contributions from individuals like you are vital to our success. They enable TSRI's pioneering researchers to continue to advance the understanding of life-threatening diseases such as Parkinson's, cancer, diabetes and HIV; speed delivery of new medicines; and, ultimately, deliver a cure. On behalf of everyone at TSRI, thank you for your support.

Enjoy the new issue of *Endeavor,* and let me know what you think!

PETE SCHULTZ, PH.D. / PRESIDENT, TSRI

MEET YOUR BOARD

This spring, TSRI appointed 11 new education, business and scientific leaders to its Board of Directors. Paired with the unique and extensive expertise of its existing members, TSRI's new Board of Directors will be critical to the advancement of the Institute's vision of advancing basic scientific research and rapidly translating new discoveries into life-saving medicines for the public benefit.

John Diekman, Ph.D., will serve as chairman of the new board, replacing retiring Chairman Richard A. Gephardt, whose insightful leadership and steadfast support over the past seven years was invaluable to the organization.

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

TSRI PROFESSOR JIN-QUAN YU. PHOTO BY JOHN D. AND CATHERINE T. MACARTHUR FOUNDATION.

The Journey of Jin-Quan Yu, Ph.D.

MACARTHUR FELLOWSHIP WINNER

Jin-Quan Yu didn't expect to win the $625,000 "genius grant" from the MacArthur Foundation. In fact, when the Foundation rang his cell phone last August to inform him of the award, he didn't even take the call.

He was too busy thinking and talking about chemistry over lunch with a fellow TSRI chemist. Seeing the Chicago-area number of the caller, Yu suspected it was his leasing company calling about a car payment. It took several further calls to both his cell and office phones before he reluctantly picked up and learned the surprising good news.

Yu's remarkable ability to focus on chemistry and screen out all distractions is probably one of the reasons he earned the award. Known formally as a MacArthur Fellowship, it is given out every year — without warning; one cannot apply for it — to a small group of scientists, artists and others who are deemed by their most accomplished peers to "show exceptional creativity in their work and the prospect for still more in the future."

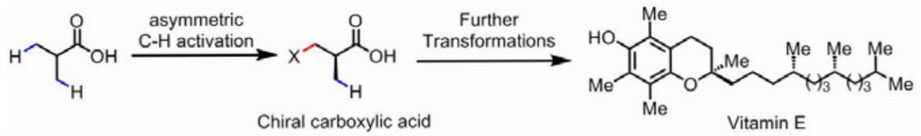
"Exceptional creativity" has been and continues to be the hallmark of Yu's work. For years, he has conceived of one big innovation after another in organic synthesis — the science (and the art) of designing chemical reactions to build useful organic molecules.

"Exceptional creativity" has been and continues to be the hallmark of Yu's work.

by

JIM SCHNABEL

The synthetic chemist's ideal — almost alchemical in its ambition — is to transform the cheapest, most ordinary chemicals into lifesaving drug molecules or other highly valuable products. In pursuit of that ideal, Yu has invented dozens of methods for what chemists call C-H activation. This seemingly simple step in molecule-building involves pulling a hydrogen (H) atom off the carbon (C) atom skeleton of an organic molecule and replacing that hydrogen with a more reactive cluster of atoms called a functional group — often the key ingredient that makes a new molecule useful.



A GRAPHIC FROM THE YU LAB ILLUSTRATES HOW C-H ACTIVATION CAN BE USEFUL FOR CONVERTING FEEDSTOCK INTO MEDICINE. IN THIS CASE, THE ACTIVATION PRODUCES VITAMIN E.

C-H activation is much more challenging than it appears, and methods for achieving activation were quite limited until recently. In fact, much of the progress in the past decade has come from Yu and his lab.

In a 2010 paper in the journal *Science*, for example, he and his colleagues unveiled a new C-H activation method for coupling two large classes of organic molecules known as aryls and olefins — an improvement over a textbook reaction.

Yu's many other novel C-H activations have allowed chemists to turn inexpensive, structurally simple chemicals into a broad variety of molecules that are otherwise hard to build — and are of great interest to the pharmaceutical industry.

Having blazed this trail, Yu is now a sought-after speaker at academic and industrial institutions worldwide. Several pharma companies, including Bristol-Myers Squibb, Vertex, Pfizer and Boehringer Ingelheim, have established relationships with his lab and have eagerly adopted many of his new reactions for ongoing drug discovery and development programs.

The MacArthur Fellowship is just one of many prizes and accolades he has earned; others include the Sackler Prize, the Mukaiyama Award, and fellowships in the American Association for the Advancement of Science and the Royal Society of Chemistry. Yu's own life bears an uncanny resemblance to the modern synthetic ideal, for it too involves a transformation of the ordinary into the extraordinary.

Yu was born in the remote mountains of Zhejiang Province, one of China's least developed regions. His parents, like most of their generation in the mountains, essentially did not have the opportunity to learn to read. The nearest schools didn't offer much, and students often quit after a few years of education to work in local fields or mines.

Yu's many other novel C-H activations have allowed chemists to turn structurally simple chemicals into a broad variety of molecules that are otherwise hard to build.

The timing of Yu's birth, 1966, was just as inauspicious as the place, for in that same year Chinese leader Mao Tse-Tung and his supporters proclaimed the Cultural Revolution. This political movement against "intellectuals" soon shuttered high schools and universities across the country and sent tens of millions of students into the rice fields for "re-education" or turned them into slogan-shouting Red Guards. "Up to the mountains, down to the villages!" proclaimed vast red banners in every Chinese city.

Yu was already so far into the mountains that, as he said, "I never even heard of the Cultural Revolution when I was a little kid." But for as long as it persisted, the shutdown of higher education closed off any opportunity for improving his life through academic achievement.

The small house where Yu grew up with his older brother and his parents was, unusual even for rural China, miles from the nearest village. It had no electricity or running water. To get water, Yu and his brother would fill buckets from a nearby spring. The family principally lived off the small garden they had planted near the house — its centerpiece a beloved pear tree — as well as a small share of the local collective farm's produce. But even salt was a luxury; to obtain it, the boys would often walk 10 miles to the coal mine where their father worked, gather empty salt sacks from the mine's small store, soak them in water at home, and then boil off the water to yield the precious crystals of sodium chloride.

Yu's elementary school was in the next valley — a two-hour walk each way. "It involved going up over a mountain and then down again, and across a river by boat," he remembered.

In the winters, the snow was often deep.

Because he didn't live in the same village, the other children bullied him. But the teacher liked him. He was the only student who always did his homework, always knew the material, and somehow, despite his arduous daily journey — even through the snowy winters — always turned up.

Where did Yu get his drive and aptitude? The hardships of life in the mountains were certainly one motivator. His parents continually urged him to do better in school, with the aim of enabling him to one day leave behind the poverty of the mountains and the farm work that he disliked. Yu's father had chronic health problems — he succumbed later to a coal-related lung ailment—and for this reason, Yu as a boy began to dream of becoming a doctor.

Yu suspects too that the plainness of his early life and his wild surroundings — the absence of distraction — ultimately gave his intellect more space to develop when confronted by academic tasks that interested him.

> "What I mostly saw in my childhood were mountains, water, birds, fish, my dog. To this day, I feel I have a simple mind that is often not very good at tasks outside chemistry," he said.

By building their house in a secluded valley, contrary to the collectivist norm of communist China, his parents also revealed a striking independence of mind that Yu seems to have inherited, which may be one of the keys to his creativity as a chemist.

Whatever he had going for him, the odds against his escaping the rural life and making a name for himself remained steep.

But luck was on his side. In 1976, when Yu was 10, Mao died and with him, the Cultural Revolution. The government set up programs to improve education in rural areas and began screening rural schools for children with high aptitude.

At the age of 13, Yu scored high on one of the screening tests and suddenly — never having been out of the mountains before — was sent down from his valley to attend a special school in the lakeside town of Qiandaohu.

"It was the first time I saw a bicycle. The first time I saw paved roads. The first time I saw a basketball," he remembered.

The students of this special school were kept there — with short breaks for home visits in winter and summer — for an accelerated, three-year high school-level education focused on math, physics, chemistry and Chinese literature. Yu once again distinguished himself through his aptitude and his attitude.

"There were many kids there who had not lived as remotely as I had, whose lives were more modern, more social, and as a result, they always seemed distracted by many things," he recalled. "I just didn't have those distractions; I seemed much more able to focus."

Toward the end of the third year, Yu and his fellow students underwent the two-day ordeal of the gaokao, the national university entrance exam, the importance of which is akin to the American SAT — squared. Of those taking it that year, only a small percent scored high enough to attend college.

Yu passed, and although his biology score was too low to permit entrance to medical school — unsurprising, since he had never taken a biology course to speak of — he was accepted as a chemistry major at East China Normal University in Shanghai.

His first big chemistry feats came only a few years later. At the Guangzhou Institute of Chemistry, where he obtained his master's degree, Yu developed reactions for making perfumes that brought the Chinese government a significant amount of hard-currency income. That won him a British-Chinese scholarship to attend Cambridge University, where he earned his Ph.D. in the laboratory of biosynthesis expert Jonathan Spencer, Ph.D.

During his four years at Cambridge, Yu co-authored numerous papers on how natural enzymes catalyze molecule-building reactions in cells. But by 2000, he was convinced that organic synthesis — building organic molecules with step-by-step reactions in flasks, not with enzymes or cells — offered more flexibility, more opportunity for innovation.

His next stop was the Mecca of organic synthesis, the Harvard laboratory of Nobel laureate Elias James "E.J." Corey, Ph.D. There, Yu decided to explore an area of research where even the world's best organic chemists had made only incremental progress: C-H activation.

"I was an outsider, and I sensed that if I just did what everyone else was doing, I wasn't going to win," he said.

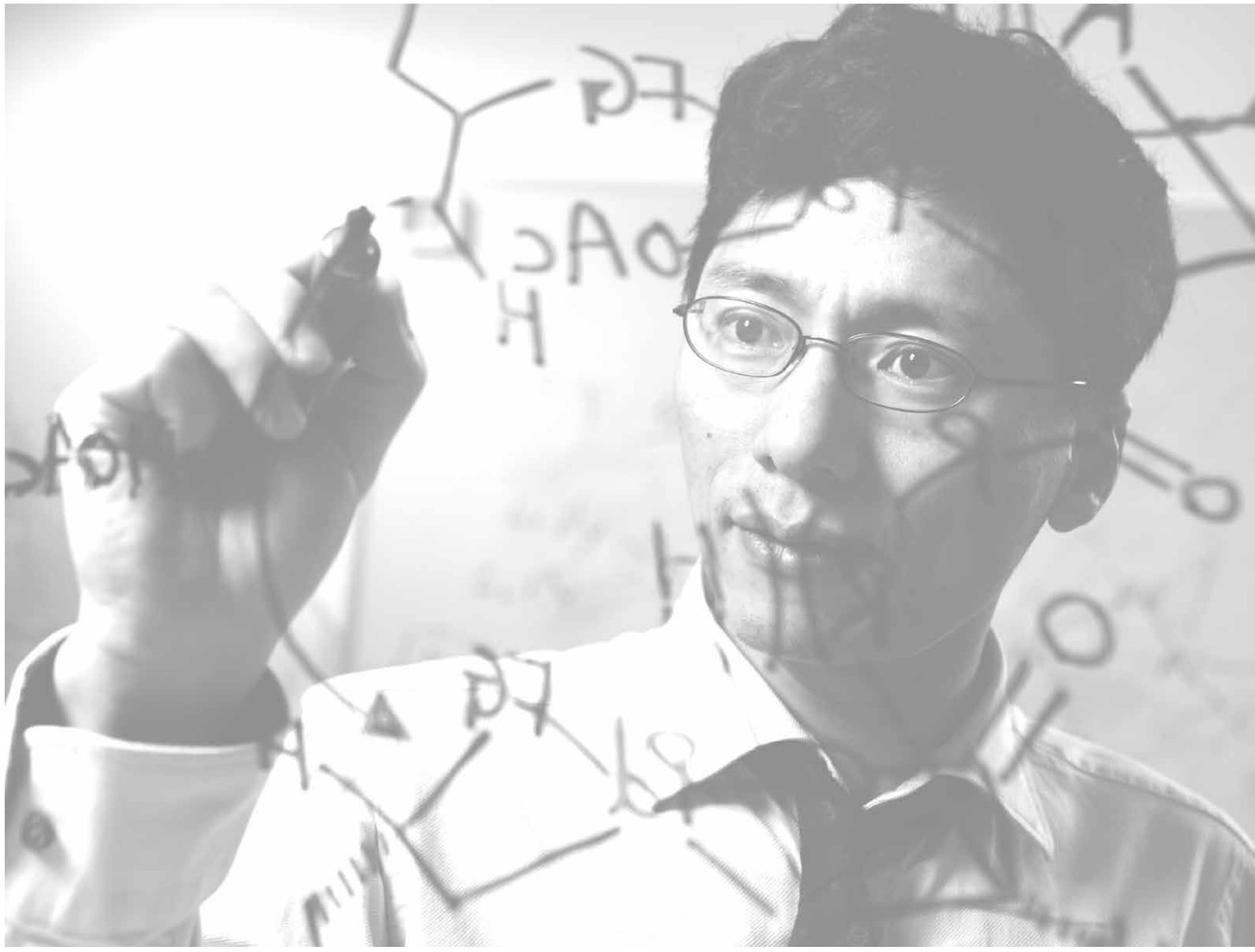
TSRI chemist Phil Baran, Ph.D. — another organic synthesis wunderkind who, in 2013, won his own MacArthur Fellowship — first met Yu when they were postdoctoral students together at Corey's laboratory. He remembered an Einstein-like character with wild hair and "a mind like a sponge."

"Jin had an intuition into reactivity that was unique — I knew I could learn something from him," Baran said.

In 2006, only a few years after joining TSRI, Baran invited Yu — then an assistant professor at Brandeis University — out to La Jolla to give a talk on his C-H activation research. He urged TSRI's then-president Richard Lerner, M.D., and others to attend. "I didn't really have any influence at TSRI then," Baran said, "but I knew that my elder colleagues were phenomenal scientists who would recognize good science when they saw it."

They did, and soon hired Yu, who became a full TSRI professor just three years later.

YU'S RESEARCH IS CHANGING CHEMISTRY TEXTBOOKS AND EXPANDING THE FIELD OF DRUG DISCOVERY.



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Now in 2017, the biggest theme in Yu's C-H activation research is the creation of chiral molecules, whose structures are asymmetric in a way that permits them to have distinct "left-handed" and "right-handed" forms. Each of these forms, or enantiomers, has the same chemical formula but is effectively a mirror image of the other.

For drug molecules, typically only one enantiomer has the desired properties, whereas the other is inert or even causes unwanted effects. Yet the chemistry for producing just one enantiomer of a molecule isn't easy; in fact, only a handful of textbook reactions are enantioselective. Yu's new enantioselective reactions, published in a recent flurry of high-profile papers in *Science* and *Nature*, are expected to make their way into textbooks soon, and they point to the eventual development of enantioselective reactions for virtually any kind of organic molecule.

LEFT: JIN-QUAN YU CIRCA 2013. RIGHT: A LIST OF YU'S AWARDS DATING BACK TO 1990

2016 MACARTHUR FELLOWSHIP | THOMSON-REUTERS "WORLD'S MOST INFLUENTIAL SCIENTIFIC MINDS," 2014 | ACS ELIAS J. COREY AWARD FOR OUTSTANDING ORIGINAL CONTRIBUTION IN ORGANIC SYNTHESIS BY A YOUNG INVESTIGATOR, 2014 | RAYMOND AND BEVERLY SACKLER PRIZE IN THE PHYSICAL SCIENCES, 2013 | FELLOW OF AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, 2012 | FELLOW OF THE ROYAL SOCIETY OF CHEMISTRY, 2012 | MUKAIYAMA AWARD, SOCIETY OF ORGANIC SYNTHESIS, JAPAN, 2012 | ACS ARTHUR C. COPE SCHOLAR AWARD, 2012 | BRISTOL-MYERS SQUIBB AWARD, 2012 | NOVARTIS EARLY CAREER AWARD IN ORGANIC CHEMISTRY, 2011 | YOSHIMASA HIRATA MEMORIAL LECTURESHIP MEDAL, NAGOYA, 2010 | DISTINGUISHED FACULTY AWARD OF CHINESE-AMERICAN CHEMISTRY & CHEMICAL BIOLOGY PROFESSORS ASSOCIATION, 2009 | ELI LILLY GRANTEE AWARD, 2008 | AMGEN YOUNG INVESTIGATOR'S AWARD, 2008 | SLOAN RESEARCH FELLOWSHIP 2008 | JOURNAL AWARD FOR SYNLETT & SYNTHESIS, 2006 | CAMILLE AND HENRY DREYFUS NEW FACULTY AWARD, 2004 | ROYAL SOCIETY UNIVERSITY RESEARCH FELLOWSHIP, 2003 | FELLOWSHIP OF ST JOHN'S COLLEGE, UNIVERSITY OF CAMBRIDGE (JRF), 1998 | SINO-BRITISH SCHOLARSHIP BY BRITISH COUNCIL AND EDUCATION MINISTRY OF CHINA, 1994 | PRESIDENT AWARD FOR OUTSTANDING STUDENTS OF CHINESE ACADEMY OF SCIENCES, 1990

In 2014, on a trip to China to see his mother and brother, who no longer lived in the mountains, Yu managed to visit the lonely place where he'd grown up. "I had dreamed about it for years — the last time I had really stayed there was in 1987," he said.

He had heard rumors that the government had torn the house down; new rules in China meant that houses without electricity or running water were forbidden as environmental hazards. So he made his way to the nearest village and then up the old track into the valley of his childhood, despite the overgrowth and the wild boar nests that had rendered it almost impassable.

The house had indeed been torn down. The garden was gone too — all but the pear tree. The surrounding wilderness was more or less as it always had been, however, and perhaps it was the most salient reminder of his origins.

"It's important to be fearless," he said. "To be truly fearless is not easy, and I feel that a part of that attitude comes from how I grew up. I never worried much about whether I would gain something or lose something, because I had nothing to start with."

ONE OF THE MANY MEDICINAL HOODS IN CALIBR'S STATE-OF-THE-ART CHEMISTRY LABS.

A New Biomedical Research Paradigm

TSRI'S ALLIANCE WITH THE CALIFORNIA INSTITUTE FOR BIOMEDICAL RESEARCH (CALIBR) OFFERS A NEW MODEL FOR DELIVERING BENCH-TO-BEDSIDE RESEARCH

Over the last few decades, scientists around the world have made impressive advances in our understanding of human biology and how to apply those learnings to improving human health. These scientific discoveries have laid the groundwork for developing better treatments or potentially even cures for life-threatening diseases. But the translation of those breakthroughs into new medicines is typically a lengthy process that requires substantial resources and technical "know how."

Research institutes and universities that have tried to accelerate this process by establishing translational capabilities *within* academic centers have been met with limited success — primarily due to the unique challenges of establishing the skills, processes and infrastructure required for translational science within a basic science environment.

Last fall, in a move that envisaged an entirely different model than "starting from scratch," TSRI and the California Institute for Biomedical Research (Calibr) came together in a first-of-its-kind non-profit research alliance that integrates the strengths of both organizations — basic research (TSRI) and translational capabilities (Calibr).

The new TSRI/Calibr affiliation will allow basic scientific discoveries made at TSRI to move much more quickly through the high-risk "translational gap" of preclinical and early-stage clinical testing via the expertise of Calibr — one of the most advanced translational institutes in the world. Drug candidates in later stages of clinical validation are more likely to attract biopharma partnerships for ongoing Phase 2 and 3 clinical trials — increasing the potential for 1) novel medicines to reach patients faster than ever before and 2) better licensing revenues to the Institute that can be reinvested back into basic and translational research — a game-changing model for funding non-profit research.

by

JIM SCHNABEL

The emergence of this new model is attributable to the vision of Peter Schultz, Ph.D., the founding CEO of Calibr and TSRI's president who, in addition to working as an academic scientist, has been heavily involved in innovative technology and translational research.

An accomplished chemist with a doctoral degree from Caltech (1984), Schultz had founded and was still involved with three biotech companies when he came to San Diego from UC Berkeley to join TSRI as a professor in 1999.

That year, Schultz also founded the La Jolla-based biomedical research organization the Genomics Institute of the Novartis Research Foundation (GNF). Schultz's vision for GNF was to build state-of-the-art technologies that would both accelerate and lower the cost of basic and translational research, then apply those tools to the development of innovative new human therapeutics. GNF grew quickly and was so successful at delivering assets that it soon became a major contributor to the Novartis drug pipeline across a number of therapeutic areas ranging from cancer and autoimmune disease to metabolic and infectious diseases. But as GNF grew to roughly 600 staff in 2010 (six times larger than originally anticipated), the pressure to integrate GNF into Novartis also grew.

Based on the belief that the technologies and processes developed at GNF could be extended to a more academic setting, Schultz began to conceive of a different type of translational research organization that would be like GNF but more nimble, more autonomous and with a non-profit mission that would allow the team to consider unmet needs regardless of commercial interests and pursue any number of paths forward for drug development — be it outlicensing, a spin-out company, a pharma partnership or engagement with another non-profit organization.

"A major founding principle of Calibr was independence," said Matt Tremblay, Ph.D., who had been both a postdoc in the Schultz lab and a principal investigator at GNF. He is now Calibr's chief operating officer and vice president of business development at TSRI. "The ability to partner with anyone or advance any idea that could impact human health without scrutinizing the business case was incredibly intriguing to many of us who had been trained and worked under Pete. Plus, we had learned so much about finding and hiring the right 'type' of scientists who thrive in that kind of environment; we were confident we could do much more with much less."

The challenge? Funding.

At GNF, the close link with Novartis meant funding was never really an issue. But for a new non-profit translational institute that wouldn't be tied to just one pharma sponsor, finding the money to pay for dozens of scientists and a building full of sophisticated equipment was going to be a central challenge.

Fortunately, Schultz had many strong relationships within the pharma world, including one with Peter Kim, M.D., then Merck's head of research and development.

"Peter Kim had a lot of respect for Pete, and thought Calibr was a great idea," said Jim Schaeffer, Ph.D., Calibr's vice president, external relations, who at the time was one of Kim's top "scouts" for promising academic projects.

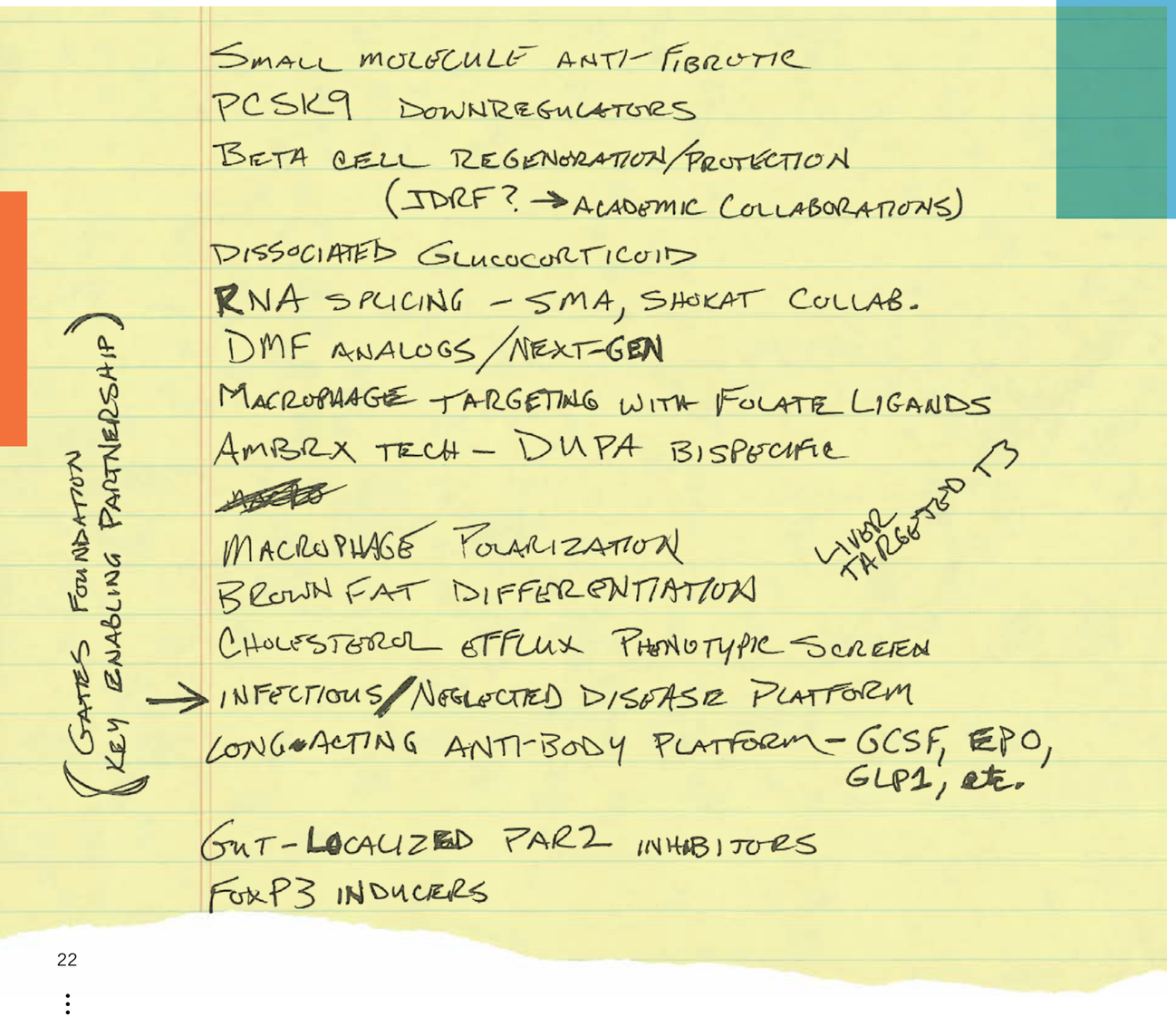
In early 2012, Merck agreed to give Calibr not just start-up funding but a relatively long-term commitment of support, totaling nearly $60 million over four and a half years. In return, Merck got a look at whatever Calibr was doing, and, if it liked a project that was meeting its goals, had the first right to negotiate to formally take it into its own drug development pipeline.

With funding and high expectations in place, there was only one thing for Calibr to do: get started. "There were no people, no equipment and no space — we had to become operational very quickly," said Schaeffer, who served as Merck's primary liaison to Calibr during the start-up phase.

The new institute rented temporary space; acquired high through-put screening equipment and libraries from a company Schultz had previously founded, as well as inexpensive secondhand laboratory equipment; and began hiring, starting with several Schultz postdocs and GNF mentees, including Arnab Chatterjee, Ph.D., Luke Lairson, Ph.D., Tremblay, Feng Wang, Ph.D., and Travis Young, Ph.D.

"There were five or six of us who moved over from GNF and TSRI to lead groups of young scientists and put Pete's vision into practice. We recruited aggressively and got the lab up and running with long hours and team work," remembered Tremblay. "At the same time, we were also setting up numerous projects, many of which came directly from Pete's lab or simply from Pete himself."

FROM THE TOP: PETE SCHULTZ, ARNAB CHATTERJEE, LUKE LAIRSON, MATT TREMBLAY, FENG WANG AND TRAVIS YOUNG.



"Literally, in our first three-hour meeting with Pete, we made a list of 60-70 projects, some ongoing in his lab, some just stream of consciousness out of his head," said Tremblay.

Calibr's start-up team divided the work into therapeutic areas, assigning each team member more than a half-dozen separate projects. In an academic basic science setting, that would have been a virtually impossible management burden given the diversity of tools and expertise that would have been required for so many investigations. But translational science tends to concentrate its investigators' activities in just a few areas, such as compound screening, medicinal chemistry to optimize compounds, and preclinical tests to establish safety and target engagement. Thus, a suitably equipped and staffed translational research facility can run many more projects, more quickly, than a basic research facility of similar size — and this was particularly true of Calibr.

AN EARLY LIST OF CALIBR'S DIVERSE RESEARCH PROJECTS

"Calibr's breadth of projects, in terms of both disease areas and therapeutic approaches, was and remains unique," said Chatterjee, director of medicinal chemistry. "Not just in terms of making new drug molecules across multiple therapeutic modalities and identifying really interesting drug discovery opportunities, but also taking molecules that are already known and have somehow stalled because of a significant technical challenge, and using creative ideas to address those challenges."

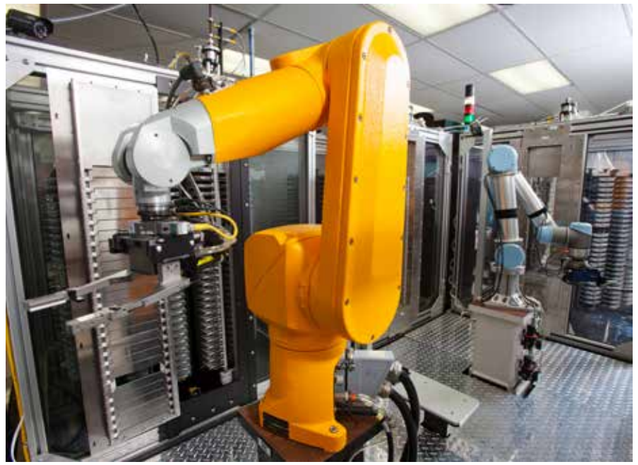
Young, a principal investigator, agrees. "That's what makes Calibr special, exciting and every day a challenge. The diversity of research here is probably greater than just about anywhere else with the same number of people."

Merck's funding alleviated the immediate need to secure additional sponsors, enabling Calibr's management team to focus on staffing and meeting meaningful endpoints for many of its projects. But the idea had always been to preserve a measure of independence by maintaining diverse sources of funding. By the end of 2012, with Calibr installed more permanently in a 35,000-square-foot facility in La Jolla, the team began to cultivate other relationships.

"Helping Pete implement his vision for Calibr was both invaluable and extremely exciting. We all had the feeling that we were contributing to something that would have a tangible positive impact on human health."

— LUKE LAIRSON, PH.D., CALIBR

LUKE LAIRSON AND
PETE SCHULTZ CIRCA 2014



CALIBR'S HIGH-THROUGHPUT SCREENING CAPABILITIES AND INFORMATICS TOOLS ARE CENTRAL TO DRUG DISCOVERY AND OPTIMIZATION EFFORTS

The first new collaboration they struck was with the Juvenile Diabetes Research Foundation (JDRF), which had forged a drug development partnership with GNF during Schultz's tenure and was familiar with most of the initial Calibr team.

"We knew we could help them in a broader way than we had been able to at GNF, because we could partner with the best academic scientists in their network to move their research forward into drug development and thus better leverage the JDRF investment," said Tremblay.

After striking an initial agreement with JDRF, the Calibr team expanded their model to encompass diseases of the developing world and reached out to the Bill & Melinda Gates Foundation.

In April 2014, after several meetings and briefings, including between Schultz and Bill Gates himself, the Bill & Melinda Gates Foundation committed $30 million in funding (an amount that has since grown) — largely giving Calibr the freedom to pursue what it saw as the most compelling opportunities in neglected disease drug discovery and to adapt to changing global health needs, such as viral outbreaks. This was followed by funding from the California Institute for Regenerative Medicine (CIRM), Wellcome Trust and others.

These agreements demonstrated that translational research could be funded through non-traditional means, such as partnerships and philanthropy. The Merck agreement had contractually limited Calibr from entering into sponsorship agreements with other commercial entities as long as Merck was continuing to fund Calibr at such high levels. Thus, the deals with JDRF and the Bill & Melinda Gates Foundation helped Calibr maintain its independence.

In March 2013, Peter Kim stepped down as head of research at Merck and was replaced by former Amgen research chief Roger Perlmutter, Ph.D., who opted to wind down funding for Calibr. Schultz persuaded Perlmutter to spread the remaining funding commitment beyond the planned four and a half years — until 2019 — and allow Calibr to directly engage other commercial partners.

And it soon did. In late 2014, Bristol-Myers Squibb (BMS) in-licensed an advanced drug candidate from Calibr aimed at treating fibrosis, a scarring condition that can affect the lungs, kidneys and other organs.

"That was a turning point," said Tremblay. "BMS reviewed and ultimately licensed the fibrosis compound as they would an advanced asset from a venture-backed biotech company. It changed our expectations of what Calibr could become."

The following year, Calibr struck another deal with Pfizer for an advanced antibody-based treatment for heart failure. Pfizer entrusted Calibr with the running of a Phase 1 clinical trial and funded new Calibr employees who possessed extensive experience in clinical trial design and management — further validation for Calibr's high-quality leadership and capabilities.

While these additional pharma-supported projects were important for keeping Calibr funded and busy, Schultz and his team were already moving the Institute toward a new model.

At the end of 2015, Schultz agreed to take on the leadership of TSRI. His dual role at Calibr and TSRI enabled a clear view of the strengths and needs of both organizations — sparking the idea of bringing both institutes together to create a bench-to-bedside model that both advances research and directly impacts the public with new medicines for unmet needs.

By integrating the two organizations, Calibr could more closely connect to one of its most fruitful sources of academic projects, and TSRI would have an easier-than-ever translational outlet for its scientists. Moreover, by moving molecules into clinical development where they are significantly more valuable and attractive to biopharma, Schultz hoped to create a new model for funding non-profit research institutes in which the licensing revenues from these assets are reinvested into basic and translational research, relieving the dependence on federal funding.

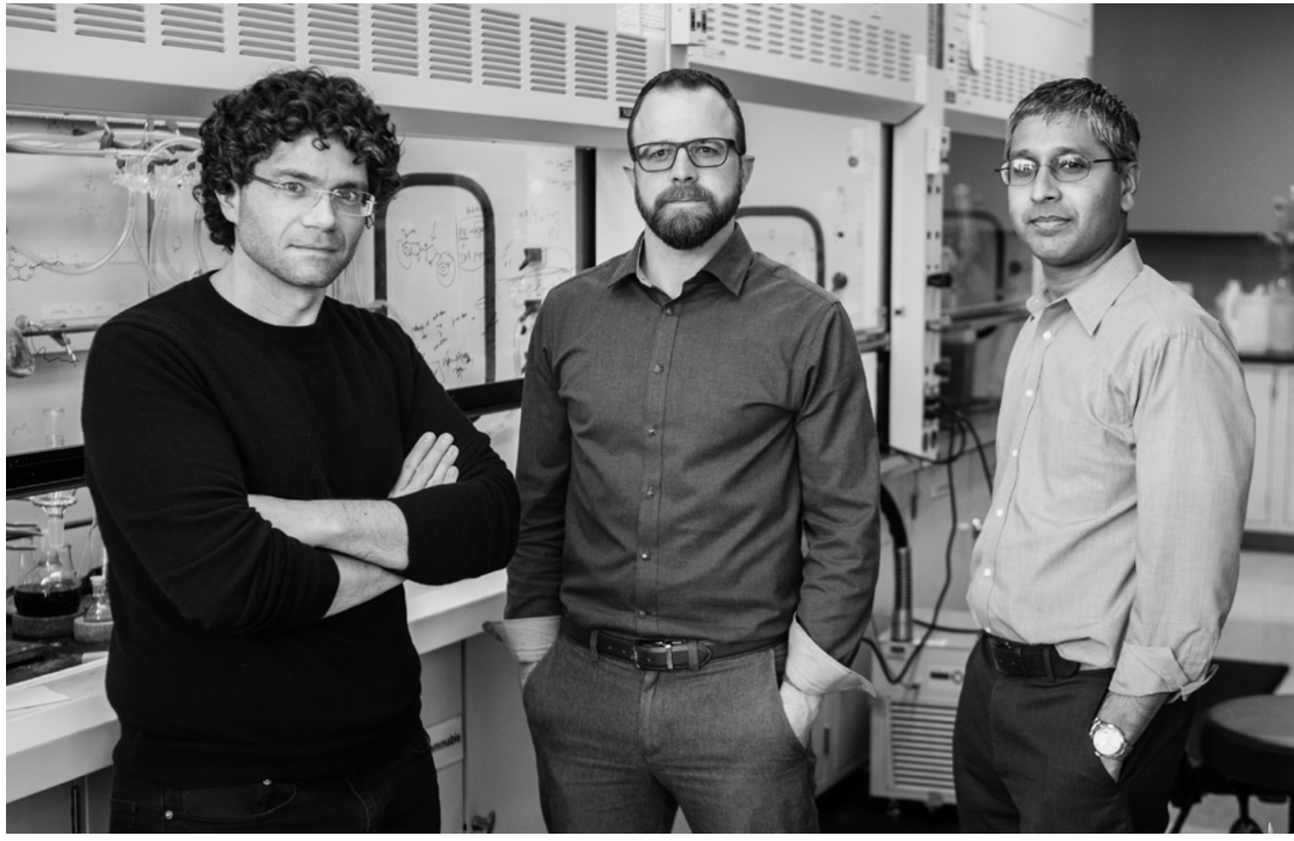
The alliance has already yielded a pipeline of eight innovative candidate medicines poised to advance into initial human clinical trials, which Schultz plans to support through a unique philanthropic initiative. (See PRIMER sidebar.)

"These early clinical stage activities (e.g., demonstration of safety and proof-of-concept studies) will provide the critical data needed for pharma and biotech companies to commit substantial resources to the costly later stages of drug development and regulatory filings required for drug approval – all of which means we can impact the lives of people living with life-threatening diseases much faster," said Schultz.

"In an environment of dwindling federal funding and escalating costs, the potential to generate an evergreen source of financial support for non-profit research represents a potential paradigm shift for research.

"We are incredibly excited by the possibilities to both influence scientific discovery and impact patient lives worldwide."

MATT TREMBLAY, TRAVIS YOUNG AND ARNAB CHATTERJEE IN ONE OF THE LABS AT CALIBR



CREATING AN EVERGREEN FUNDING MODEL

Despite impressive advances in our understanding of human biology, new medicines are still desperately needed for diseases ranging from childhood illnesses and neglected diseases to cancer and the degenerative diseases of aging.

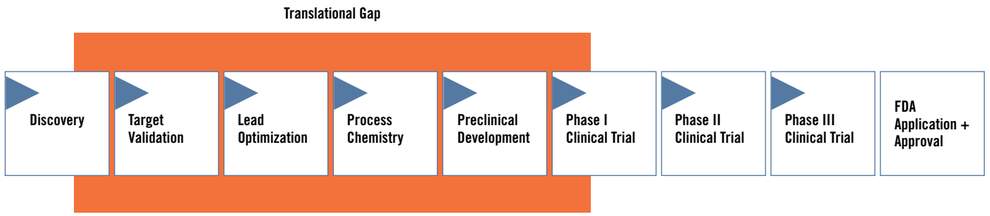
As part of the TSRI/Calibr alliance, the two organizations have established a new research model designed to accelerate bench-to-bedside drug discovery efforts while also creating a self-sustaining, evergreen funding source for ongoing research.

An integral feature of this new model is the PRIMER (Program-Related Investments in Medicines and Evergreen Research) Fund — a unique funding vehicle designed to move a portfolio of promising drug candidates into Phase 1 safety and/or proof-of-concept trials. These include new medicines for degenerative diseases of aging, cancer, lung and autoimmune disease and pain. This portfolio approach helps ensure that the overall success of the program (and the ability to reinvest) is not dependent on the outcome of any given program.

The PRIMER Fund will utilize program-related investments (a form of charitable investment) from private foundations, public charities and individuals (acting through donor-advised funds) as seed funding for most of the preclinical research. The Fund offers contributors the potential to recoup their original investment (which can be redeployed as charitable distributions), as well as a modest return on investment. Remaining revenues will be reinvested in other TSRI/Calibr research projects — providing for the future development of life-saving medicines.

> “ This approach not only serves the public by accelerating the development of new medicines that directly impact patients, it also acts to create a consistent and perpetual funding source for critical early-stage biomedical research.”
>
> — PETER G. SCHULTZ, PH.D., TSRI PRESIDENT

The advancement of basic research discoveries through the preclinical phase (or translational gap) and into early clinical studies often is hindered by lack of funding, incentives or technical expertise. By demonstrating clinical safety or early indications of efficacy, PRIMER increases the likelihood of uptake by commercial partners, thereby accelerating the initiation of remaining clinical studies and speeding the delivery of new medicines to patients around the world.



TWO-SIDED APPROACH TO TREATING CANCER

Several ongoing Calibr projects involve the development of “bispecific” antibodies as advanced anticancer therapies. A normal antibody is a protein of the immune system that binds one specific antigen. A bispecific antibody is engineered in such a way that it engages two different targets (antigens) simultaneously.

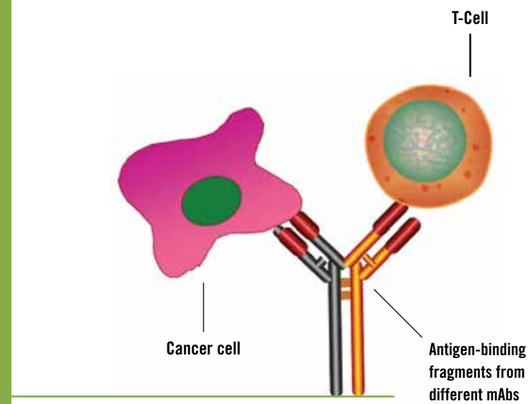
Bispecific antibodies can be designed so that one part of the antibody binds with a tumor-specific molecule on cancerous cells, while the other attaches to and helps activate healthy cytotoxic T-cells, which in turn can kill the malignant cells. With funding from Wellcome Trust, Calibr is currently developing a bispecific antibody as a potential treatment for prostate cancer.

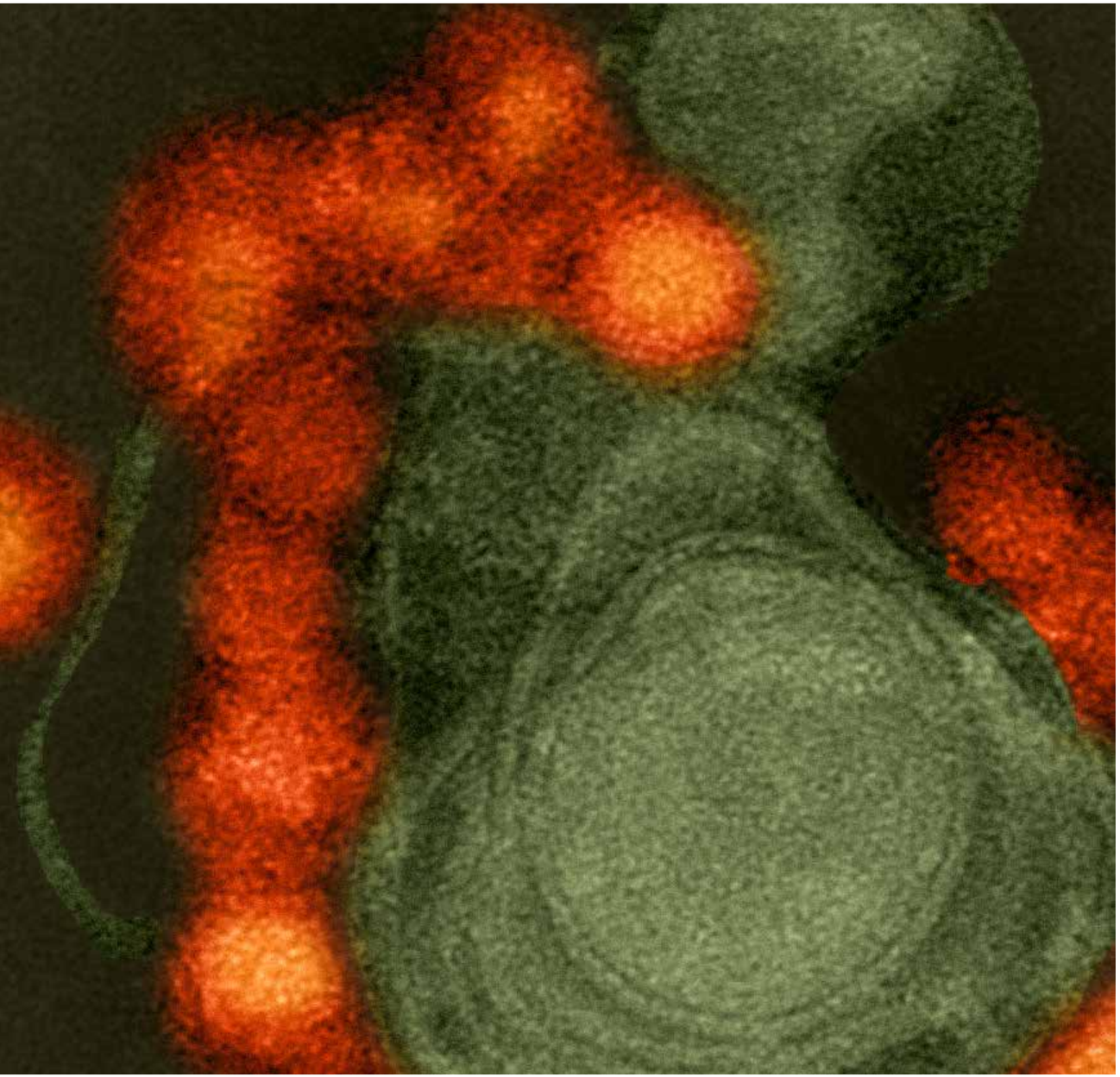
A similar bispecific antibody strategy can be used to tune the activity of powerful T-cell-based cellular therapies called chimeric antigen receptor T cells (“CAR-T” cells). CAR-T cells have demonstrated promising results in clinical trials, offering some patients whose leukemia had been resistant to multiple other therapies a complete cure. But it is often associated with serious side effects. With funding from the National Institutes of Health, the U.S. Department of Defense, and The American Cancer Society, Calibr is making antibodies that act as “switches” for CAR-T cells, and are designed to turn them on and off at will and spare patients some of the dangerous side effects of this potent cancer therapy.

“We expect that our ‘switchable’ CAR-T cell technology will be able to treat a wide variety of cancers, including blood cancers such as leukemia and lymphoma, and solid breast and pancreatic cancers,” said Travis Young, who heads up several bispecific antibody projects at Calibr.

> “ The development of this universal platform could be a game-changer for cellular immunotherapy by improving patient outcomes, bringing down treatment costs and expanding patient access.”
>
> — TRAVIS YOUNG, PH.D., CALIBR

A bispecific anitbody is an engineered protein composed of antigen-binding fragments from two different monoclonal anitbodies





TRANSMISSION ELECTRON MICROSCOPE IMAGE OF ZIKA VIRUS

Zika: A Dangerous Virus Challenges Scientists to Work Quickly

Sixteen days after conception, a human embryo's neural tube emerges. Its curved column of cells transforms in stages and bursts, week by week, into an entire nervous system — a spinal cord, peripheral nerves, and at the apex, more than 100 billion specialized cells forming the brain. If all goes well, after nine months, the healthy baby will recognize its mother's voice, see her smile and communicate hunger and contentedness.

With the emergence of Zika virus, that critical developmental window is at risk. If a mother first becomes infected with Zika during pregnancy, and that virus infects her fetus, entire groups of its developing neurons may die. Profound birth defects may result.

This discovery, that the Zika virus itself leads to the severe birth defects associated with the massive Zika outbreak in the Americas in 2015 and 2016, was further confirmed by scientists at TSRI in a paper published online by the journal *Nature* in October 2016. Neuroscientist Damon Page, Ph.D., and microbiologist Hyeryun Choe, Ph.D., collaborated on the work on TSRI's Florida campus.

"You see a severe hit early on to some fundamental structures in the brain," said Page, an associate professor at TSRI. "You just cannot regrow those lost neurons."

Since 2013, the World Health Organization (WHO) has counted nearly 2,600 births in 59 countries of babies born with Zika-associated microcephaly — an abnormally small, misshapen brain. Babies born infected with Zika tend to have heads that appear flattened and small. They cry inconsolably, sleep little and may require around-the-clock care.

by

STACEY SINGER DELOYE

The virus, originally named ZIKV, was first discovered in 1947 in a rhesus macaque in the Zika forest in Uganda.

TSRI ASSOCIATE PROFESSOR HYERYUN CHOE. PHOTO BY JAMES MCENTEE.

Forty-one babies with Zika-associated microcephaly have been born within the United States since the outbreak began over a year ago when WHO declared Zika a global health emergency.

The need to understand Zika's rapid spread, and why it causes birth defects in some, but not all, pregnancies, is urgent. That's why several TSRI researchers are exploring causes and potential new treatments, plus preventive strategies against Zika. While Choe and Page look for answers to how and why Zika infects cells, Professor Michael Farzan, Ph.D., and his collaborator, Associate Professor Timothy Tellinghuisen, Ph.D., are looking for treatments and potentially a vaccine.

A common daytime-biting mosquito that multiplies in puddles and discarded trash may be chiefly responsible for scattering the tiny virus across oceans and continents. Each time mosquitoes *Aedes aegypti* and *Aedes albopictus* drink blood from an infected person and later bite someone else, they can potentially inject virus along with their blood-thinning saliva. These mosquitoes favor the warm and wet conditions of the tropics and sub-tropics — precisely the conditions that make Florida a top travel destination.

On the Jupiter, Florida, campus of TSRI, Choe spends many hours pondering how and why viruses infect cells. In 2016, Choe began to pursue Zika virus — but instead of asking "Why," she asked, "Why not?"

"West Nile and dengue viruses are very closely related to Zika virus," explained Choe, an associate professor at TSRI. Both are flavi viruses — they are enveloped RNA viruses spread by mosquitoes. What's more, West Nile virus also infects neurons, yet reports of birth defects are exceedingly rare. Microcephaly isn't among them.

So why don't West Nile and dengue infect developing fetuses?

Choe suspected only Zika had found a way to cross the placenta. The organ that nourishes the developing fetus in utero, the placenta provides an effective barrier against most pathogens, she said. It brings the mother's blood supply to snuggle up next to baby's, with a membrane of just a few cells' thickness separating the two. This system allows for the exchange of gases, nutrients and wastes — but not most germs. Zika appeared to be one of the few exceptions.

To probe what made Zika different, Choe and her research team obtained a specific type of donated placental cells called human umbilical vein endothelial cells. They incubated them in culture dishes and then pipetted viral solutions onto them. The solutions included active West Nile virus, dengue and Zika viruses. They waited and watched.

"Zika, but not the other two, efficiently infected those cells," she said. She wanted to know more. "That was an important finding, but we had to figure out why."

As a widely recognized expert in the molecular biology of viral attachment, Choe had ideas about where to look.

Cells need a self-destruct mechanism to protect the larger body in case of cancer or infection. They do that, in part, by alerting the immune system to gobble them up if necessary. Some viruses, Choe and colleagues found, successfully co-opted that alert signal and used it to strengthen their ability to see, attach and enter cells. Blocking the signal slowed and weakened certain viruses, offering a new opportunity to intervene.

Viruses enter and exit cells in much the same way people enter and exit locked doors. If the right molecular key fits snugly into the right molecular lock, the door to the cell membrane swings open, allowing the virus to enter and set up its copy system. In the case of Zika, Choe established that fetal blood vessel cells in the placenta served as preferential doors for Zika virus to reach the fetus. Next, she needed to find and describe the locks.

A 2015 paper had revealed that a Zika entry "key" connected with a cell-surface "lock" called AXL on some types of skin cells. The more AXL, the more locks, and the likelier the odds of infection. Fetal blood vessel cells were studded with AXL protein "locks."

Choe and her team found that only Zika had the right "key," not West Nile or dengue, because neither dengue nor West Nile virus fits into the second component of the lock, a protein called Gas6.

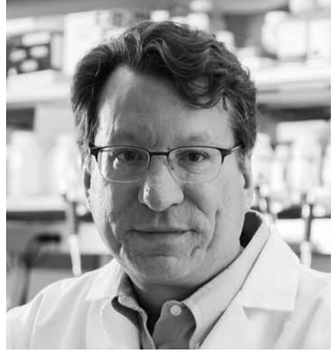
Choe's team checked their findings multiple ways, and each time the results were the same.

"If Zika is going to pass from mother to fetus, it must pass through placental barrier cells, and AXL is the entry gate on the cells that directly lead to fetal circulation," she said.

Knowing what was at stake, she and her team worked day and night and delivered the findings for publication in the journal *Proceedings of the National Academy of Sciences* before year's end.

"I hope that other scientists can use this information to work toward a cure," she said.

The first active human case of Zika virus was found in 1964.



TSRI PROFESSOR MICHAEL FARZAN. PHOTO BY JAMES MCENTEE.

A few steps away from Choe's office, Farzan is pursuing Zika on multiple fronts — antibody treatments, drugs and possibly a new type of vaccine. Farzan is optimistic. Zika is a straightforward virus that he expects won't present the same types of hurdles as HIV and dengue. Potential drugs and vaccine candidates are already emerging.

Nearby, behind a glassed-in room, a tall bank of refrigerator-like cabinets houses a library of small-molecule drugs and related compounds supplied by the National Institutes of Health and expanded upon by medicinal chemists at the Institute. The library complements a precision robotic system, like those used to build cars in Detroit. But rather than turning bolts or spraying paint, this robot conducts thousands of experiments at a time, in a process called high-throughput drug discovery. Tellinghuisen collaborates with Farzan on that line of attack. The art to the science is in devising an experiment that can be "read" by the machine, enabling the machine to easily see a hit or a miss.

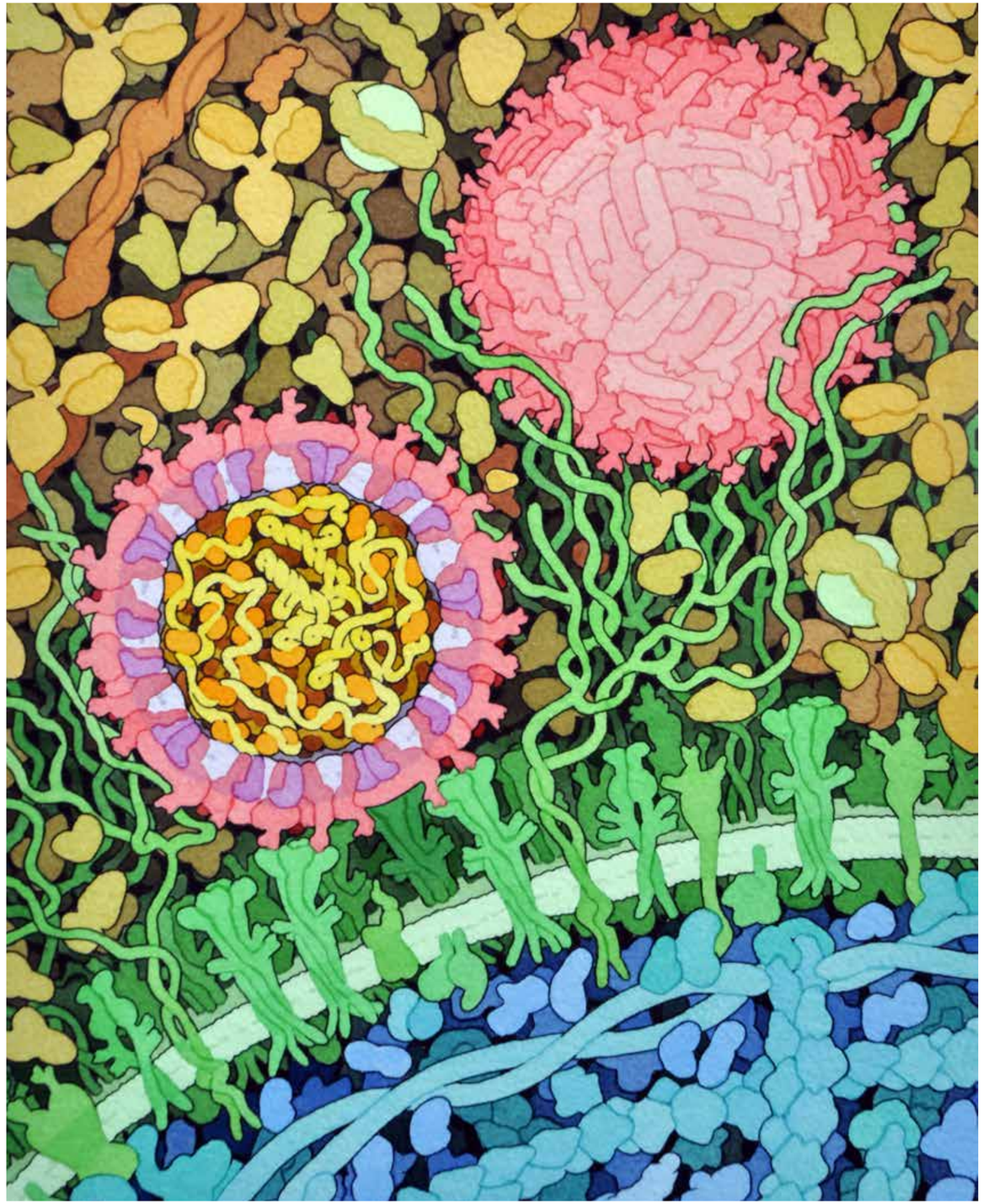
Farzan sounds a practical note of caution. A potential new drug to treat Zika in pregnant women is needed, but it would require many years of study to find enough participants, unless an existing medication with a well-known track record proves effective. Vaccine candidates will present similar safety concerns, he said. The fastest approach to thwart the spread of Zika, he believes, is to engineer a highly specific antibody or antibody cocktail that can prevent Zika from binding to key cells while not causing unwanted side effects.

"Antibodies have exceptional safety profiles and would be the only medical intervention justifiable in pregnant women in the next several years," Farzan said.

Antibodies are Y-shaped proteins manufactured by circulating white blood cells. Their wide ends are highly variable, conforming like puzzle pieces onto the binding sites of specific germs, calling in the immune system's demolition crew. Massive numbers of successful antibodies are released by white blood cells during serious illness. After the illness passes, the blood supply retains copies, leaving a living index of germs met and conquered. Scientists at TSRI and elsewhere are learning to read and take advantage of these living indexes.

80% of people who become infected with Zika virus never have symptoms.

In those who do, the most common Zika virus symptoms are fever and rash.



THIS WATERCOLOR ILLUSTRATION BY TSRI SCIENTIST DAVID GOODSELL HELPS SCIENTISTS AND THE PUBLIC UNDERSTAND HOW ZIKA VIRUS (PINK AND YELLOW) INTERACTS WITH HUMAN CELLS (GREEN AND BLUE).

Pregnant women who live in or have traveled to Zika-infested regions are vulnerable to the most serious complications from the virus — birth defects.

Farzan is collaborating with immunologist and TSRI Professor Dennis Burton, Ph.D., whose lab is employing rapid screening methods developed for antibody discovery. The scientists are collaborating with other institutions on the effort as well, including the University of Miami, where pathologist David Watkins has been collecting samples of anti-Zika antibodies from Zika patients who seek treatment there.

"I feel like the field is on its way," Farzan said.

Farzan is also engineering a new type of vaccine made from DNA, the template of genes, or RNA, the reader and copier molecules of genes.

His research offers the promise of custom-making vaccines to have desired traits, without ones that might promote other infections or cause permanent side effects.

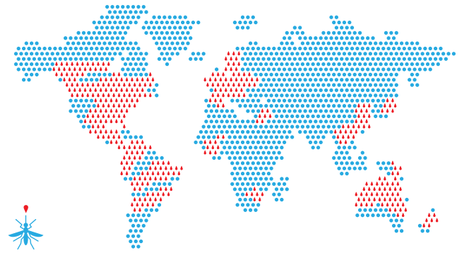
"The way you know you can vaccinate against something is that people will not get it twice. We just have to be a little bit smart about avoiding some of the dangerous consequences," Farzan said. "That is a problem we have to engineer out of it."

Fortunately, it does appear that people infected with Zika become immune. The evidence? After a truly terrible two years of rapid spread throughout the Americas, Zika's assault on pregnant women appears to be on the wane in regions like northeastern Brazil and other areas where a majority of residents have been exposed. This suggests that exposure offers immunity, though for how long is an open question.

In the United States, however, Zika is still a new virus to most people, and a serious threat to pregnant women. The Florida Department of Health released a report in January indicating that Zika is still being imported into the state and may still be spreading locally. The new rainy season will begin in May or June, when the mosquito population will be at its peak.

"We will continue to pursue the work on Zika, because it's an important problem that is not likely to go away in the near future," said Page.

What if just one pill could provide months of protection from Zika virus infection and a multitude of other diseases — even malaria and West Nile virus?



SPREAD OF **ZIKA VIRUS** WORLD MAP 2016 VISUALIZATION

EXPLORING ZIKA PROPHYLAXIS

At the California Institute for Biomedical Research (Calibr) in La Jolla, medicinal chemist Arnab Chatterjee, Ph.D., is collaborating with scientists at TSRI to develop a treatment that kills mosquitoes without affecting humans. This future treatment would need to be a highly potent, safe, long-acting small molecule engineered to pass through the host while killing the blood-thirsty insects that bite the host.

Veterinary medicine has long relied on similar principles to protect dogs and cats from ticks and parasites. Those treatments have a good safety track record — even in pregnant animals, Chatterjee noted.

Modeling suggests that if a similar type of treatment could be given to people, and the treatment stayed in their system for two months, a community's disease-spreading mosquito population could be drastically cut by as much as 90 percent. In fact, Chatterjee's team has developed a set of such molecules and is now testing and refining them.

A grant to Calibr from the Bill & Melinda Gates Foundation has enabled Chatterjee to pursue the project, with help from partners in private industry, including TropIQ in the Netherlands. Soon he hopes to launch a clinical trial in a Zika-impacted community. The findings are to be published without protecting the intellectual property so that the drug can be inexpensively made and widely distributed to protect global health.

KRISTIAN ANDERSEN OF THE SCRIPPS RESEARCH INSTITUTE AND THE SCRIPPS TRANSLATIONAL SCIENCE INSTITUTE. PHOTO BY NICK DUA.

Mapping Zika's Spread, One Mutation at a Time

The great mystery of Zika virus has been its transformation into a global menace after simmering seemingly benignly for decades in Africa and Asia, causing little observed illness.

What changed? Did the virus mutate into a great threat, or did new human behavior expose a little-known ferocity? Greater understanding could help direct more effective prevention efforts.

Kristian Andersen, assistant professor, TSRI, and director of infectious disease genomics at the Scripps Translational Science Institute (STSI), recently led a team that crafted an evolutionary atlas of Zika's entry into the United States. Their paper, which has been made available as early-access on bioRxiv, concludes that heavy traffic from the Caribbean, as opposed to traffic from Brazil, for example, could have been a dominant contributor to the localized spread of Zika in Miami. They also offer solid evidence that mosquito control can prevent Zika harm.

The clues to the Zika mystery lie within the virus itself — within its genes, he explains. Andersen's team at STSI, a collaboration between Scripps Health and TSRI, reads viral genomes the way most people read novels. They take dozens of copies of what's basically the same book, highlight the tiny differences, and map them. But first, they must sequence dozens of samples, some from mosquitoes, some from humans. The technical challenge of sequencing virus from a tiny fluid sample in a mosquito has proven especially difficult, he said.

Last year, Andersen and a global team of researchers revealed that a single mutation could have made Ebola more contagious during the outbreak that killed an estimated 11,000 people in West Africa between 2013 and 2016.

"The Zika outbreak is very different than the Ebola outbreak," Andersen said. "I think the Zika virus we have now is essentially the Zika virus we had in the past. I think it just moved into a new area with a lot of unexposed individuals."

His group sequenced viral samples from 28 of 256 individuals with Zika in Florida. As they worked, they released data publicly to assist other scientists. They found transmission happened in Florida at least four times, with three of the four linking to Caribbean strains. Andersen believes Zika may have gained a toehold in Miami as many as 40 times, but repeatedly discontinued its spread due, in part, to effective mosquito control.

Knowing this should enable more effective prevention efforts going forward, he said. It may be cost-effective for the United States to assist with mosquito control efforts in global Zika hot-spots.

"If you see it coming from one country where people travel from all of the time, then you probably want to help out there," Andersen said. "What we have today is very new; we can jet anywhere very quickly, and viruses don't respect borders."

READ MORE ABOUT ANDERSEN'S RESEARCH
http://biorxiv.org/content/early/2017/02/03/104794

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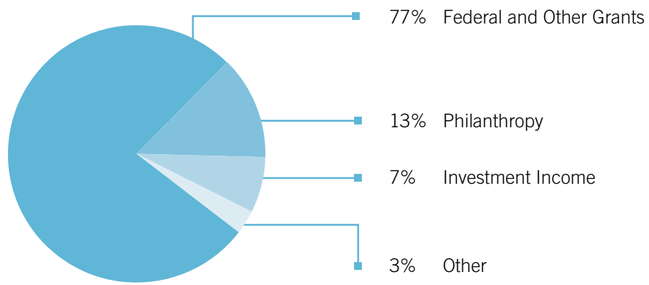
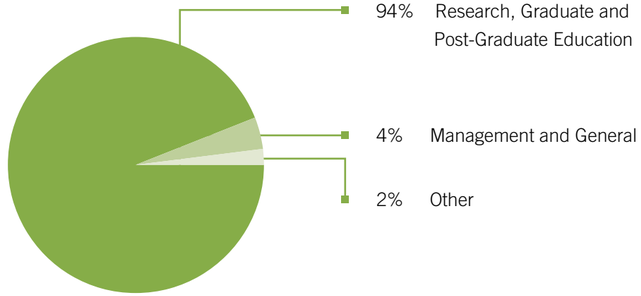
TSRI REVENUES, FISCAL YEAR 2016



TSRI EXPENSES, FISCAL YEAR 2016



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Every gift is important

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We have done our best to make this list an accurate reflection of gifts to The Scripps Research Institute from January 1, 2016 to December 31, 2016. If errors or omissions exist, please accept our apologies and contact us at (858) 784-2339 or philanthropy@scripps.edu.

Thank you,
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THE SCRIPPS RESEARCH INSTITUTE GRADUATE PROGRAM

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"One of the Top 10 programs in the nation."

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TSRI's Graduate Program was established in 1989 as an interdisciplinary school offering doctoral (Ph.D.) degrees in the chemical and biological sciences to the next generation of scientists. The program graduated its first student, Jairo Arévalo, in 1993.

This year's graduates join a distinguished group of more than 600 alumni making significant contributions to scientific innovation around the world. Collectively, they also represent the brightest young scientific minds working to understand the nature of and find solutions to such challenging (and diverse) medical needs as cancer, multiple sclerosis, malaria and HIV.

On the following pages, you will read about one alumnus who has parlayed her scientific expertise into a Hollywood career. Please look to future issues of *Endeavor* for profiles of other distinguished alumni who have leveraged their scientific training at TSRI to advance biomedical research in other exciting and impactful ways.

For more information about TSRI's Graduate Program and how you can support educational training for the next generation of scientific thought leaders, please visit http://education.scripps.edu or http://scripps.edu/philanthropy

Jairo Arévalo / TSRI's First Graduate Degree Recipient (1993)

CLASS OF
1993

Jairo Arévalo was, by all accounts, an energetic, life-long learner. Born in Colombia, Arévalo earned his bachelor's degree in microbiology at the Universidad de los Andes in Bogota, Colombia. After three years working in a local hospital, Arévalo received one of the first Colombian Presidential Fellowship awards, which landed him in the Department of Molecular Biology at TSRI in 1985. He spent four years amassing extensive postdoctoral experience conducting research, learning x-ray crystallography and expanding his knowledge of computing, but he still wanted to experience the rigors of a conventional Ph.D. program. In 1989, Arévalo became one of the pioneering students to join TSRI's Graduate Program, and in 1993, he was awarded the program's first doctoral degree.

During his tenure at TSRI, Arévalo worked in the lab of Professor Ian Wilson, Ph.D., where he defined a new standard in the study of antibody-antigen recognition — achieving innovative and groundbreaking results. "Jairo was the most enthusiastic person you could ever meet," said Dr. Wilson. "He had such a warmth and caring for others, and he was just the perfect person for our fledgling graduate program."

Arévalo passed away in 1995, but his hard work, enthusiasm and constant search for knowledge enabled him to achieve great things in the scientific arena during his relatively short, but highly impressive career.

JOVANA GRBIC,
TSRI ALUMNA AND
VOICE OF SCIENCE
IN HOLLYWOOD.

"I am very lucky to have the opportunity to put my extensive scientific training to work ..."

Reading from a Different Script

CATCHING UP WITH TSRI ALUMNA JOVANA J. GRBIC, PH.D.

The road to a career in scientific research can be arduously long and relentlessly winding, and it occasionally takes its travelers to altogether unexpected destinations. For TSRI alumna Jovana Grbic, that road landed her in Hollywood.

If you had told Grbic as a first-year graduate student on TSRI's La Jolla campus that in just a few short years she would be rubbing shoulders with the cast of the Discovery Channel's "Mythbusters," giving a TEDx talk about media fueling a passion for science, and writing and editing scripts for TV and film productions, she probably would have laughed you out of the lab.

Yet here she is, having gone from a doctoral student in the laboratory of Professor Peter Schultz, Ph.D., now president of TSRI, to WIRED's list of "168 Geeky Media People You Should Follow on Twitter."

Combining her formal training as a biological chemist with her passion for writing and entertainment media, Grbic has made a career out of helping such clients as ABC Television, the University of California, Los Angeles School of Film, the Tribeca Film Institute and Dell Computers represent science and scientists more accurately and in more authentic ways.

"The intensity of TSRI's scientific training and the opportunity to work with a wide array of scientists from different disciplines have given me the ability to parlay my experience into a communications career dedicated to exploring and portraying the challenges of scientific discovery," Grbic said.

Grbic leverages this expertise to simplify and incorporate complex scientific topics into shows, commercials and more. Recently, she contributed to two books exploring the intersection of science and popular TV and film productions, such as the hit television series *Fringe*. One of these books, *Hollywood Chemistry,* was published by the American Chemical Society, a huge honor for someone with what she describes as "chemistry roots." Both projects, which were written for a general audience, focus on how science is portrayed and integrated into the final productions.

"Scientific content and the presence of scientists have never been more prominent," she said of today's entertainment media. "Coverage of all aspects of research is a regular staple in the mainstream media. Films such as *The Martian* and *Gravity* have buoyed support for NASA funding and space exploration, while others like *Hidden Figures, The Imitation Game* and *The Man Who Knew Infinity* help imbue respect for scientists' contributions to humanity."

The majority of her consulting and communications work, however, involves media, marketing, advertising and more traditional science as it relates to the public at large. From web copy and white papers for pharmaceutical and medical device companies to scripted videos for technology firms, her work allows her to develop an endless variety of creative content that makes otherwise opaque concepts crystal clear.

The nexus for the entertainment and business sides of Grbic's work is ScriptPhd.com, home to her blog and podcasts examining topics ranging from artificial intelligence and space exploration to the portrayal of scientists (and science) in blockbuster films. With more than 100,000 unique monthly visitors, it's a powerful platform for Grbic to, in her words, "start conversations that reverberate about the issues and technology affecting our world today."

Building an unconventional career guided by her passion for science and creative writing hasn't been easy. But her graduate training at TSRI provided a significant foundation that continues to guide her today.

"TSRI's graduate program emphasizes two critical skills — independent problem solving and cross collaboration," she said. "Both of which have paid immeasurable dividends in my career, where I need to forge new paths and find novel solutions for a diverse set of clients and objectives across the entire spectrum of science, medicine, technology and media."

READ MORE ABOUT JOVANA'S JOURNEY ON HER BLOG

ScriptPhD.com

by

JEREMY PYLE

NEWS HIGHLIGHTS

Multiple Sclerosis Therapeutic Moves Closer to the Clinic
When Professors Ed Roberts, Ph.D., and Hugh Rosen, Ph.D., identified an anti-inflammation compound in 2008, they hoped it might one day help patients with relapsing multiple sclerosis (MS). Now, new Phase 3 clinical trial data from Celgene Corporation shows that the drug candidate (called ozanimod) can indeed reduce the frequency of debilitating MS relapses. The researchers are now looking forward to upcoming results from another Phase 3 trial evaluating ozanimod for the treatment of ulcerative colitis.

TSRI Teams Up with City of Hope to Treat HIV
A team of scientists led by TSRI Professor Richard Lerner, M.D., has developed a potential HIV cure. With their new method, antibodies stay tethered to human cells, protecting them from the virus. Their next step is to work with investigators at City of Hope to advance this treatment through safety and efficacy trials before it can be tested in patients.

A New Partnership to Accelerate Drug Discovery
Chemists at TSRI have partnered with Pfizer Inc. to pioneer new DNA-encoded library technology, an important tool for early-stage drug discovery research. This new technology will allow scientists to screen billions of small molecules to identify potentially life-saving drugs faster than ever before.

New Hope for Fighting Prostate and Breast Cancers
Two new studies led by Scripps Florida scientists demonstrate that a new class of drugs called small molecule RNA inhibitors can successfully target and kill prostate and breast cancers. The therapies have the potential to halt cancer growth without causing off-target side effects seen with many other cancer drugs. “This is like designing a scalpel to precisely seek out and destroy a cancer — but with a pill and without surgery,” said Professor Matthew Disney, Ph.D., who led both studies.

TSRI Addiction Expert Takes National Stage
Kim Janda, Ph.D., Ely R. Callaway, Jr. Professor of Chemistry at TSRI, was invited to speak at The Clinton Foundation Health Matters Annual Activation Summit in April as part of a panel moderated by former President Bill Clinton. Addressing Summit attendees — and a large audience of online participants — Janda shared how a vaccine developed in his TSRI lab could help people with opioid addiction avoid relapse and even survive potentially fatal overdoses.

Mimicking Nature to Build Better Drugs
TSRI chemists have developed a new method for mimicking nature’s molecule-building abilities more efficiently and affordably. The method allows scientists to synthesize a molecule without accidentally creating that molecule’s mirror image. With this technique in hand, Professor Jin-Quan Yu, Ph.D., believes scientists can speed up their search for life-saving medicines. In fact, he’s already working with industry scientists to test the method.

AWARDS + HONORS

TSRI has been named the Best Biomedical Science Research non-profit organization in the United States by GHP, a United Kingdom-based publication covering human, animal and environmental health.

The Boehringer Ingelheim Foundation presented **TSRI President Peter G. Schultz, Ph.D.**, with the Heinrich Wieland Prize, one of Germany’s most prestigious scientific awards. The award honors Schultz’s contributions to combining biology and synthetic chemistry and groundbreaking work in expanding the genetic code.

The American Association for the Advancement of Science (AAAS) named **James Paulson, Ph.D.**, the Cecil H. and Ida M. Green Chair of Chemistry and chair of the Department of Cell and Molecular Biology, and Professor and Howard Hughes Medical Institute Investigator **Ardem Patapoutian, Ph.D.**, as fellows.

Benjamin Cravatt, Ph.D., professor and co-chair of the TSRI Department of Molecular Medicine, has been selected by the Medicinal Chemistry Division of the American Chemical Society (ACS) as the 2017 winner of the Robert M. Scarborough Award for Excellence in Medicinal Chemistry. Cravatt was also named the 2017 winner of the ACS Chemical Biology Lectureship Award.

Jeffery W. Kelly, Ph.D., Lita Annenberg Hazen Professor of Chemistry and co-chair of the TSRI Department of Molecular Medicine, received the American Institute of Chemists (AIC) 2017 Chemical Pioneer Award for his leadership in the discovery of tafamidis, the first drug approved by regulatory agencies to slow the progression of familial amyloid polyneuropathy.

Associate Professor **Katrin Karbstein, Ph.D.,** has been named a Howard Hughes Medical Institute Faculty Scholar, a new national distinction recognizing outstanding early-career scientists who bring innovative approaches to the study of biological problems.

Associate Professor **Kristin Baldwin, Ph.D.**, received a 2016 Pioneer Award, part of the NIH High-Risk High Reward (HRHR) Research Program, recognizing highly creative and exceptional scientists with bold approaches to major challenges in biomedical research. Baldwin’s research aims to develop improved methods to study human neurobiology and disease.

Pearson Family Chair Professor **Barbara Mason, Ph.D.**, received the Brinkley Smithers Distinguished Scientist Award from the American Society of Addiction Medicine (ASAM). Mason’s work focuses on the neurobiology of alcoholism and the potential for prevention and treatment.

Phil Baran, Ph.D., and Ardem Patapoutian, Ph.D., have been elected to the prestigious National Academy of Sciences for their “distinguished and continuing achievements in original research.” The two join several other TSRI scientists as members of this exclusive group of scientific scholars.

NIH

Over the last six months, TSRI scientists have been awarded a number of new grants from several branches of the National Institutes of Health (NIH) designed to spark innovative research and bring promising discoveries closer to helping patients.

$207 Million for History Health Study — The program seeks to engage one million or more U.S. participants in a historic medical research effort, called the Precision Medicine Initiative, aimed at improving the ability to prevent and treat disease based on individual differences in lifestyle, environment and genetics.

Computational Biology ($6.6 Million) — Three groups at TSRI have been awarded grants to develop methods for computational modeling and to apply them to cutting-edge systems in biology and health. These new developments in computational biology are crucial for visualizing how cells and drugs interact.

First-of-its-Kind, Eight-Year, $5 Million Grant for Biology of Memory — Ron Davis, Ph.D., chair of the Department of Neuroscience on the TSRI Florida campus, was awarded a $5 million Outstanding Investigator Grant, one of the first of its kind, by the NIH and the National Institute of Neurological Disorders and Stroke (NINDS). His lab's research will focus on the biological processes that underlie memory formation, targeting the brain mechanisms and genes that mediate forgetting and how the brain organizes memories.

Breast Cancer Research ($3.3 million) — Professors Ben Shen, Ph.D., and Christoph Rader, Ph.D., have been awarded up to $3.3 million to create the next generation of breast cancer treatments for the thousands of patients whose current treatment options are limited. The researchers aim to develop a potent type of therapy that combines the specificity of antibodies, which attack only cells they recognize, with a highly toxic payload designed to kill specific cancer cells with far greater efficiency than most currently available treatments.

$2.5 Million to Explore 'Click Chemistry' Applications — TSRI's K. Barry Sharpless, Ph.D., and Peng Wu, Ph.D., were awarded two new grants of approximately $1.9 million and $640,000 for projects focused on "click chemistry." Created in the mid-1990s by Sharpless, click chemistry is a method for the rapid discovery of new chemical properties by reliably "clicking" molecules together.

Developing Drugs for Heart Disease and Rheumatoid Arthritis ($1.8 million) — Scripps Florida scientists have been awarded approximately $1.8 million to develop a series of drug candidates for diseases including heart disease, rheumatoid arthritis and several neurodegenerative disorders. The co-principal investigators of the three-year project are TSRI Professor William R. Roush, Ph.D., and Associate Professor Derek Duckett, Ph.D.

$4.8 Million to Advance HIV Vaccine — TSRI Professor Michael Farzan, Ph.D., received $4.8 million in funding through a 2017 Avant-Garde Award for HIV/AIDS research from the National Institutes of Health's National Institute on Drug Abuse (NIDA). The new funding will support a five-year project, led by Farzan, to improve the safety of a potential HIV vaccine, bringing it closer to human clinical trials.

Support for the Development of Memory-Altering Medications for Addiction — Initial funding of $640,000 has been awarded to Scripps Florida researchers to investigate how drug-related memories can be safely erased to reduce the risk of drug relapse. "We're excited that the NIH recognizes the outstanding potential of our research," said study co-leader Associate Professor Courtney Miller, Ph.D. "Now our research is on an accelerated footing toward clinical trials."

OTHER

Muscular Dystrophy Association Support for Drug Development
The Muscular Dystrophy Association (MDA) has awarded $300,000 over three years to Matthew Disney, Ph.D., professor on the Florida campus, for further work to optimize two novel drug-like compounds for treating ALS and a form of muscular dystrophy called myotonic dystrophy. These diseases are currently incurable, but Disney's laboratory is working to develop small molecule drug candidates that can potentially remove the source of the disease from affected cells.

TSRI'S NOBUYOSHI SUTO. PHOTO COURTESY AGOSTINO MELA.

Nobuyoshi Suto, Ph.D.

TSRI biologist Nobuyoshi Suto conducts innovative research into how brain circuits motivate our behavior. His work has led to interesting insights into what might drive a person to relapse into drug addiction. When he's not in the lab, however, Suto is a jazz pianist and composer. He has performed around the world and released eight jazz albums under the name Nobu Stowe. *Endeavor* sat down with Suto to ask how he found harmony between science and song.

How did you end up in these two different fields?

I was 18 and just starting college when I came to the United States from Japan, and I was really interested in rock music — mostly The Beatles at that time. Honestly, I really wanted to be a rock star. But I couldn't tell that to my parents, so I came up with the idea that I would study psychology at UC Berkeley, where the psychologist Timothy Leary — famous for the 60s counterculture slogan "turn on, tune in, drop out" — studied the kinds of psychedelic drugs that The Beatles were into.

What drew you to neuroscience?

As I learned more about psychology, I started to wonder about experiments like Pavlov's dogs, where dogs learned to associate the sound of a bell with food. I was curious about where the brain stores these associations between environmental cues and behavior.

I'm interested in the biological basis of motivation. That's the reason I majored in psychology and have focused on studying drug addiction. Understanding the brain circuits involved in addiction gives us an interesting window into the basic relationship between abnormal or exaggerated motivation and brain activity.

by

MADELINE MCCURRY-SCHMIDT

What do you find most fascinating about this work?
Well, this is a cliché, but the brain is very complex. As scientists, we are trained to reduce such complex machinery into smaller parts. But, at the same time, the "parts" or individual brain activities need to be understood as a whole. We also need to understand each individual's behavior within the context of their environment.

For example, almost all drugs of abuse increase the neurochemical dopamine, but that's not the only reason people become addicted or even use drugs for recreational purposes. It's more informative to understand a person within the whole cultural context — for example, there's a cultural expectation that you'll drink wine at a dinner party.

What made you want to join TSRI?
This is an incredibly fertile scientific environment. TSRI boasts a diverse group of world-class scientists, each specializing in different cutting-edge technologies — making a truly multidisciplinary project possible. I obviously don't have all the necessary experience with all different techniques, like pharmacogenetics or mass spectrometry, so I rely on the expertise of colleagues, like TSRI faculty Friedbert Weiss, Ph.D., and Pietro Sanna, M.D. The diversity of available resources and the ease of collaboration here have really helped to extend and enrich my research portfolio.

How did you end up playing jazz?
I was in a rock band during college, and we did get some recording offers, which I foolishly turned down — because I thought we should wait for a contract with Sony! I was into progressive rock in high school and college, then turned to jazz in graduate school.

Who inspires you in music?
My hero in jazz is pianist Keith Jarrett because he seems to seamlessly mingle different elements in music. And when I think about it, the way I structure my research is kind of like that. Some people really specialize in their research — and that's great! But I'm interested in bringing together different disciplines, like traditional psychology and molecular biology.

Do you think the creativity you use in jazz has a role in science?
Yes! Creativity is the key for both music and science. You need to know the fundamentals, but you also need to think "outside the box."

What is performing on the road like? Seems like an interesting contrast to lab work.
Well, I never made it big enough in music to experience the glamorous life on the road, like private jets and first-class hotels. But I was fortunate to be invited to jazz festivals in Europe. Just like attending a scientific conference, it's always a pleasure to meet musicians, journalists, promoters, organizers and fans with different backgrounds. As in science, a good collaboration is an important ingredient for success in music.

What kind of music do you like to listen to in the lab?
I cannot listen to music and work. I start thinking like a musician and it's too distracting!

SUTO FOCUSES ON COLLABORATIONS AND COMBINING UNEXPECTED MUSICAL STYLES.

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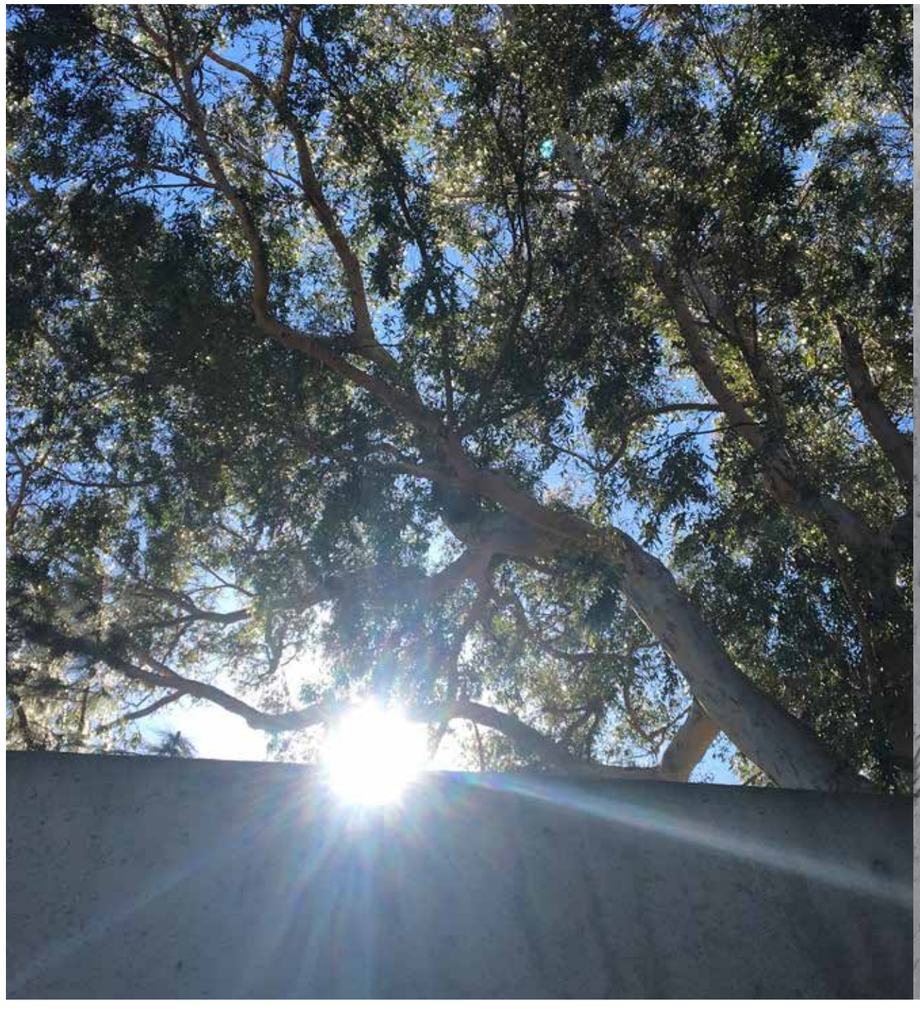

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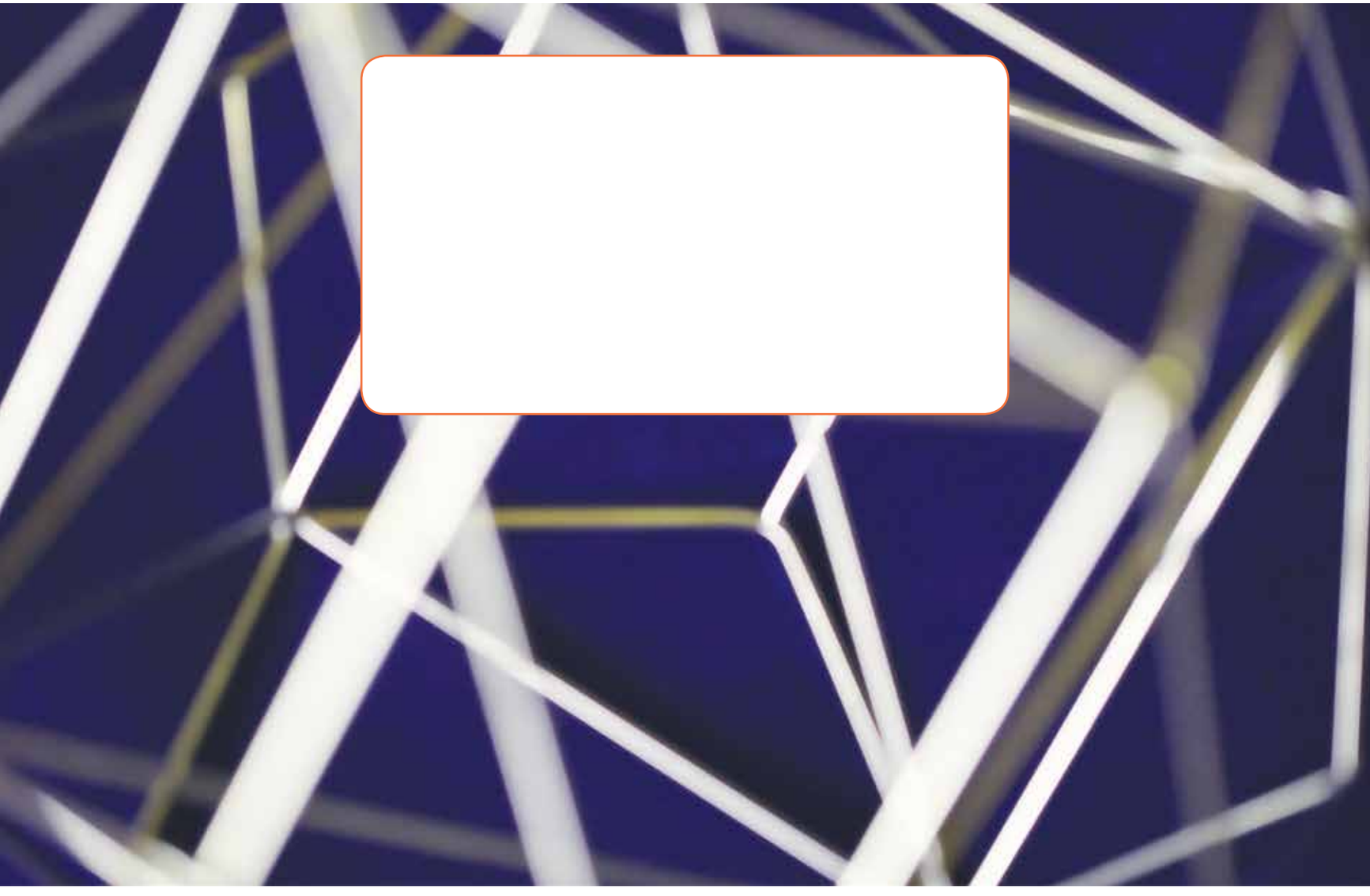

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