INSIDE STANFORD MEDICINE

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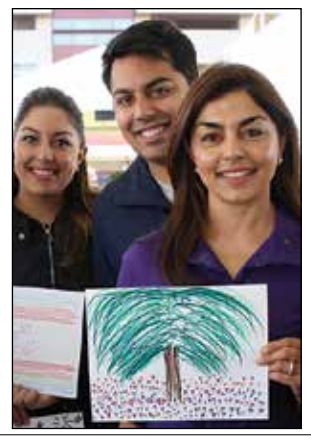

Drawings are being collected and will be assembled into a digital mosaic depicting the new hospital that will open in 2019.

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New grad students welcomed with lab coats

By Julie Greicius

Andy Renteria's parents had never been on a plane before. But Renteria bought airline tickets to fly them from his rural hometown in Emporia, Kansas, to the Bay Area to join him at the PhD lab coat ceremony at the Stanford School of Medicine.

The ceremony, which was held Sept. 24 at the Li Ka Shing Center for Learning and Knowledge, served as an official welcome for new graduate students in the Stanford Biosciences, which spans 17 different departments and interdisciplinary programs across the university.

The event was sponsored by the by the Office of Graduate Education, Stanford Medicine Alumni Association and the Office of the Dean of the School of Medicine.

"My journey to Stanford feels especially meaningful because I was able to get here despite certain disadvantages, which many students who are underrepresented in STEM, and grad school in general, also face," said Renteria, using the acronym that denotes science, technology, engineering and mathematics. "I also personally feel emotional about being here because I know my parents are proud of me and the value I placed in my education to reach this point."

GEORGE NIKITIN

William Talbot helps Kenisha Puckett into her lab coat Sept. 24 at a ceremony welcoming graduate students in the biosciences. Lila Hope, right, is president of the Stanford Medicine Alumni Association.

Welcoming students

William Talbot, PhD, the medical school's senior associate dean of graduate education and postdoctoral affairs, welcomed the new students, their families and friends.

"We're truly delighted that you have joined us, and we all hope that you share this excitement as you begin your journey," Talbot said.

Lloyd Minor, MD, dean of the School of Medicine, was unable to attend the ceremony in person, but a video with his welcome message was played at the event. Minor described the white lab coat as a powerful symbol of commitment to "the better understanding of the most basic building blocks of life and of the foundational science that informs so much of what we do." Breakthroughs in foundational science, Minor said, have the power not only to expand our understanding but "to open up whole new fields of research."

Lila Hope, PhD, president of the Stanford Medicine Alumni Association, told the students that their fellow alumni were there to support them. "Like everyone else here on campus, the alumni body is here for you as you go through your graduate school journey through multiple mentoring events, getting together, and just to be there for you and letting you know, even *we* made it despite what happened to us during grad school," she quipped.

Hope then encouraged students to recognize themselves as the standard-bearers of science. "It's important to remember as a member of the scientific community, you are the most crucial advocate, champion, safeguard and gatekeeper of truth and impartiality of your own experimental findings and scientific discoveries," she said.

The ceremony's alumnus speaker was David Bilder, who earned a PhD in developmental biology in 1997 at Stanford. Bilder, a professor of molecular and cell biology at the University of California-Berkeley, echoed Hope's point about the lab coat being a symbol of community.

"Community is not an instinctual value for many scientists," Bilder said. "Many times in grad school, you'll find yourself — it's basically just you and the bench, maybe in some corner of the Beckman Center late at night, losing track of the world around you and just trying to figure out through your thoughts and experiments what nature is trying to say."

And yet "knowing that you are a member of this larger community is really a profound experience," Bilder said, adding that just by being a biologist, a student participates in the achievements of all biologists. That community, he said, begins with the circle of classmates on campus and extends to the circle of Stanford faculty out to the larger circle of scientists around the world, as well as into past centuries.

'Seize this chance'

Students in the biosciences are entering "a spectacular field that is continuously revo- See CEREMONY, page 6

Tallness may be risk factor for varicose veins, research finds

By Tracie White

The taller you are, the more likely you are to develop varicose veins, according to a study led by School of Medicine researchers that examined the genes of more than 400,000 people in search of clues to what causes this common but little understood condition.

"Genes that predict a person's height may be at the root of this link between height See VARICOSE, page 7

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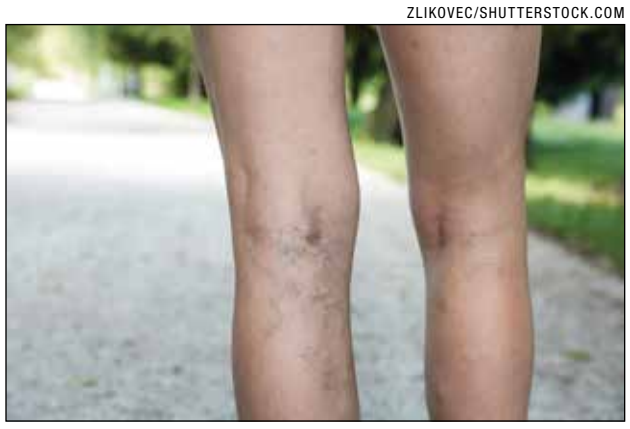


Varicose veins affect 30 million people across the United States.

Mehlika Toy, globe-trotting decision scientist, seeks solutions to hepatitis B

By Kimber Price

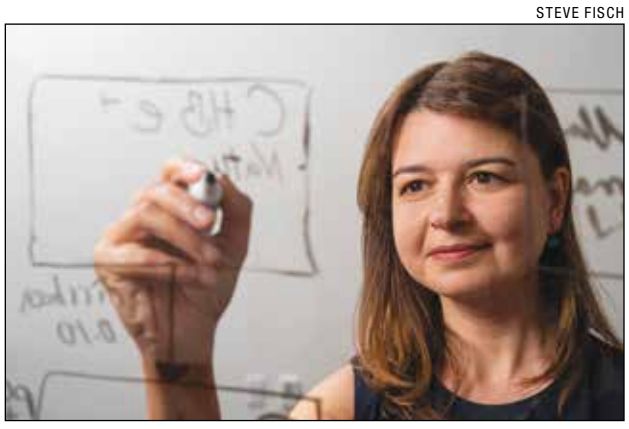
Even as a young girl, Mehlika Toy followed health and health care stories on the news. She was especially fascinated by reports of influenza and other outbreaks around the world. The Netherlands, where she grew up, has an extensive and successful screening and vaccination program, which is probably one reason why Toy was so interested in how disease could spread in other parts of the world.

Toy, PhD, now a scientist at the Asian Liver Center at the Stanford School of Medicine, has spent the last dozen years trying to figure out the best ways to control infectious disease, particularly chronic hepatitis B. The virus is often asymptomatic and spreads via blood and bodily fluids. It can lead to death by cirrhosis or liver cancer.

Although the virus is preventable with vaccination and treatable with antiviral medication, 800,000 deaths per year worldwide are attributed to undiagnosed or untreated hepatitis B. In the United States, an estimated 1.3 million people have chronic hepatitis B, yet two-thirds don't know it. Diagnosing more cases of chronic hepatitis B in order to monitor or treat the disease is the best strategy to prevent its spread.

Toy has emerged as a leading authority on the cost-effectiveness of hepatitis B treatment and care and has influenced health care policy around the world. She was chosen to develop a mathematical model for the World Health Organization to use as a tool to calculate country-specific interventions for eliminating the public health burden of hepatitis B by the year 2030.

STEVE FISCH



Mehlika Toy focuses her research on finding ways to halt the spread of infectious disease, particularly chronic hepatitis B.

"Mehlika has a great rapport with others in the field, which helps with her success, as this kind of work is something you cannot do alone," said David Hutton, PhD, associate professor of health See TOY, page 7

Mutations point to possible drug targets for heart disease, diabetes

By Hanae Armitage

From the DNA of nearly 300,000 veterans, scientists have singled out a handful of genetic mutations that not only govern levels of cholesterol, but may also inform the development and use of drugs for cardiovascular disease and diabetes, according to researchers at the School of Medicine and the Palo Alto Veteran Affairs Health Care System.

Scientists zeroed in on three mutations that disrupt the function of their respective genes. That might sound bad, but in this case, it's actually beneficial, as veterans who carried one of these mutations showed improved cholesterol profiles in their blood and a decreased risk of either heart disease, abdominal aortic aneurysms or diabetes, depending on the gene mutation.

"The idea is to use genetic data linked to electronic health records from a very large number of individuals to find genetic variants that simultaneously improve lipid profiles and protect against cardiovascular disease," said Tim Assimes, MD, PhD, associate professor of cardiovascular medicine. "From there, you can figure out what the best potential drug targets are."

All three of the main genes pinpointed in the study — PDE3B, PCSK9 and ANGPTL4 — could one day be targets for the treatment of either heart disease, abdominal aortic aneurysm or diabetes, respectively. The mutation in PDE3B, however, is the most intriguing, Assimes said, because there's already a drug on the market, called cilostazol, that mimics the beneficial mutation in that gene. Assimes said cilostazol may now also be a strong candidate for treating heart disease.

The study was published online Oct. 1 in *Nature Genetics*. Assimes is the senior author. Derek Klarin, MD, clinical fellow in surgery at Harvard, and Scott Damrauer, MD, assistant professor of surgery at the University of Pennsylvania and the Corporal Michael Crescenz VA Medical Center in Philadelphia, share lead authorship.

The power of many

To reliably identify the molecular factors that influence cholesterol levels in blood, Klarin, Damrauer and Assimes turned to the power of numbers. Through the Million Veteran Program, a national research initiative based at the Veterans Health Administration that aims to identify the genetic determinants of health and disease among U.S. veterans, the scientists pooled genetic information with cholesterol readouts from 297,626 veterans and looked for variants that play a role in cholesterol levels. The study confirmed 188 previously known genetic markers of cholesterol and identified 118 new ones.

The scientists subsequently chose to home in on a narrow sliver of rare genetic anomalies for further analysis through a technique called phenomewide screen, or PheWAS. They already knew these gene mutations affected cholesterol but wondered whether the mutations could likewise affect the risk of other diseases. The PheWAS technique gleans disease risk information from immense databases of genetic information linked to electronic health records.

Tim Assimes

Drugs as mutation copycats

Three gene mutations found through the screen piqued the investigators' curiosity. Each mutation swayed the veterans' cholesterol levels favorably, but differed in how it affected their risk for other diseases: the PDE3B mutation protected against heart disease; the mutation in PCSK9 not only decreased the risk for heart disease, something that was already known, but also the risk of abdominal aortic aneurysm; and ANGPTL4's mutation dampened the risk for Type 2 diabetes.

> Zeroing in on three mutations that disrupt the function of their respective genes.

"All of these mutations are loss-of-function variants, meaning they either substantially diminish or stop the function of the gene altogether," Klarin said. That makes a good case for developing a drug that copies what the mutation does; if a faulty PDE3B gene decreases risk for heart disease, it could be promising pharmaceutical inspiration. In this study, the PDE3B mutation was associated with lower triglycerides, higher HDLs and a 20 percent lower risk of heart disease.

"Amazingly, there's a cheap, generic drug that I already use to treat my patients for vascular disease which also mimics the effects of the mutation in PDE3B on cholesterol levels, but no one has paid attention to these 'side effects,'" Damrauer said. The drug is typically only used to treat the symptoms of blockages in leg arteries to improve how far people with vascular disease can walk without pain. The next step is to investigate whether that same drug could wear multiple therapeutic hats.

'Misled before'

Although this work may help identify new targets to curb heart disease, Assimes cautions against requesting a prescription for cilostazol for solely that purpose.

"The genetics help suggest that this drug can decrease the risk of heart disease by lowering triglycerides, but it's not proof," he said. "I would not prescribe it until a large randomized trial is completed with cilostazol or a related drug looking specifically at heart disease outcomes."

"We've been misled before by drugs that had effects on cholesterol, but they turned out to be cosmetic," he added. "Better cholesterol profiles can look great, but if the drug doesn't affect the outcome you're aiming for, which is heart attack in this case, then it's useless."

Assimes is hoping that won't be the case with cilostazol.

As for the other two genes, PCSK9 and ANGPTL4, Assimes said that further investigation of is are also needed. Several inhibitor drugs that mimic the effects of the PCSK9 mutation are already on the market to reduce the risk of heart attacks. The question is whether their use will also lead to fewer aneurysms. Drugs that mimic the effects of the ANGPTL4 mutation are still under development, and large-scale testing in humans has not yet begun.

Other Stanford co-authors of the study are professor of genetics Hua Tang, PhD; associate professor of medicine Jennifer Lee MD, PhD; former postdoctoral scholar Jin Li, PhD; and professor of medicine and Million Veteran Program co-principal investigator Philip Tsao, PhD.

Assimes is a member of the Stanford Cardiovascular Institute and the Stanford Child Health Research Institute.

The research was supported by the Department of Veterans Affairs and the National Institutes of Health.

Stanford's Department of Medicine also supported the work. **ISM**

Visibility, inclusion and connection are goals of first LGBTQ+ Forum

For Stanford Medicine's lesbian, gay, bisexual, transgender, queer/questioning community and their allies and colleagues, a new event aims to increase visibility, celebrate diversity and encourage an inclusive environment.

The inaugural Stanford Medicine LGBTQ+ Forum is set for 3:30 p.m. Oct. 10 in Berg Hall at the Li Ka Shing Center for Learning and Knowledge. The community-building event, which is free, welcomes students, trainees, staff, faculty and alumni from the School of Medicine, Stanford Health Care and Stanford Children's Health.

Registration and information for the event are available online at https://stan.md/2DKj9mI.

Timothy Keyes, an MD-PhD student at the School of Medicine, is the founder of the event, which was developed based on input from more than 200 members of the Stanford Medicine community. "I hear from people who feel like they're the only person who identifies as a sexual or gender minority in their department or in their entire program," Keyes said. "It turns out, there are a lot of us here, but we don't really have a lot of opportunities to connect with one another."

Faculty leaders for the event are James Lock, MD, professor of psychiatry and behavioral sciences; Marcia Stefanick, PhD, professor of medicine and of obstetrics and gynecology; and Yvonne Maldonado, MD, senior associate dean of faculty development and diversity and professor of pediatrics and of health research and policy.

The forum will feature personal and professional stories from LGBTQ+ members of the Stanford Medicine community, as well as networking activities, refreshments and giveaways. **ISM**

Stanford Child Health Research Institute will host inaugural symposium on Nov. 16

Registration is now open for the inaugural Stanford Child Health Research Institute Symposium, which will highlight the latest developments in maternal and child health research across the campus.

The event, scheduled for Nov. 16 at the Li Ka Shing Center for Learning and Knowledge, is free and open to Stanford community members and the public. For more information or to register, visit http://med.stanford.edu/chri/events/symposium.html.

"We invite the community to join us and learn about the cutting-edge research happening within the maternal and child health community at Stanford University," said Anthony Oro, MD, PhD, professor of dermatology and co-director of the institute. "At this inaugural event, we will hear from incredible investigators who are advancing groundbreaking discoveries that improve the health of mothers and children around the world."

Sean Morrison, PhD, director of the Children's Medical Center Research Institute at the University of Texas Southwestern Medical Center, will be the keynote speaker. He earned his PhD in immunology at Stanford and is an expert in cancer stem cell biology and metabolomics.

The symposium also will feature 19 other speakers and moderators who have been funded through CHRI programs and its campus partners.

Attendees will learn about innovative research funded by institute; funding programs and educational resources available to researchers; and investigators who are making an impact in maternal and child health. The symposium will include poster sessions and networking opportunities throughout the day.

Following closing remarks, attendees can interact with speakers in a speed-dating style gathering hosted by former Stanford participants of the Eureka Institute for Translational Medicine, an institute partner that provides professional development courses for the translational medicine community. **ISM**

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STANFORD MEDICINE

Q&A Measure F and the impact on Stanford Health Care

Voters in the City of Palo Alto will see an initiative on their ballots this November that has significant implications for Stanford Health Care.

If approved by voters, the initiative, known as Measure F, would limit the amount that health care providers in Palo Alto can charge commercially insured patients to 15 percent above the provider's "direct" costs for patient care.

The measure would apply to Stanford Health Care, Palo Alto Medical Foundation and other medical clinics in Palo Alto, as well as local doctors, dentists, optometrists and small, specialty clinics.

Stanford has taken a position officially opposing Measure F "because it would threaten Stanford Health Care's ability to provide top-quality health care to patients from Palo Alto and across the region," according to a university statement. The Palo Alto City Council recently voted unanimously to oppose the initiative. The university also opposes the similar Measure U in Livermore, where Stanford Health Care operates ValleyCare Medical Center.

Stanford Report *asked David Entwistle, president and chief executive officer of Stanford Health Care; Mary Hawn, MD, chair of the Department of Surgery in the School of Medicine; and Randy Livingston, the university's vice president for business affairs, chief financial officer and liaison for Stanford Medicine, for their perspectives on Measure F.*

Q: In a region with such a wide range of hospitals and clinics, what is Stanford Health Care's role?

Entwistle: Stanford Health Care is the only level-1 trauma center between San Francisco and San Jose, and specializes in the treatment of rare, complex diseases and disorders including cancer treatment, organ transplantation, neurosciences, cardiovascular health, orthopedic surgery and other surgical services.

As a world-class academic medical center, we draw patients not only from our region, but from around the world. They come to our campus for the innovative, high-quality care that only we can deliver. Patients turn to Stanford Health Care when it matters most to them, and our doors are always open, regardless of personal circumstances. We work with patients to ensure they get the care they need, when they need it.

Q: How would Measure F impact Stanford Health Care?

Entwistle: If passed, Measure F would require Stanford Health Care to pay rebates to insurance companies for charges to commercially insured patients more than 15 percent above the cost of "direct" patient care.

A critical subset of additional expenses covered by providers, including facilities operations, technology costs, management expenses and other types of necessary overhead, could not be factored in to the cost of care under this initiative. Measure F also fails to account for the losses that providers incur when they treat patients insured through Medicare and MediCal and those who aren't insured. Today, providers recover these losses in part through the care they offer to commercially insured patients.

Such a policy is estimated to reduce Stanford Health Care's budget by 25 percent — requiring significant cutbacks and the possible closure of many services and programs that are essential to high-quality health care in the local area.

This type of drastic restructuring would fracture our high-quality patient care models — forcing reductions of our indispensable health care team members. These reductions may include physicians, nurses, clinicians, educators, managers and others who help patients and their families cope with the difficult issues that accompany serious illnesses and injuries. It would also force us to reconsider how to use the new hospital building that is slated to open next year and eliminate our ability to retrofit current facilities. It would also threaten our status as a top academic center that supports research and education.

I want to emphasize: This initiative actually does nothing to limit the prices charged to patients with insurance coverage. Nothing in the initiative improves health care quality or patient safety. And nothing makes care more accessible to low-income and vulnerable groups.

Measure F was developed and promoted by Service Employees International Union-United Healthcare Workers West (SEIU-UHW). The measure poses far-reaching, negative consequences for a broad range of health care providers, the Palo Alto city government and, ultimately, the patients and people we care about and serve.

Q: Why has the university taken a position on this initiative?

Livingston: It's important first to understand that Stanford deeply values and respects the broad diversity of opinion and viewpoints in our community. As a general principle, the university takes institutional positions on external political matters only when they directly affect the mission of the institution itself. We believe Measure F clearly does.

Measure F threatens Stanford's commitment — through Stanford Health Care — to serve our community. It strikes at the heart of the charge in our founding grant to "promote the public welfare." High-quality health care is clearly a significant part of what Stanford contributes to the region we live in. We hear often from members of the community how highly they value having an institution like Stanford Health Care in their community.

On top of that, our own campus community of faculty, students and staff depends on the availability of high-quality health care in the immediate local area, both through Stanford Health Care and other providers. Access to this health care for the people of our community is critical to the university's success. We believe it's clear that this measure would force Stanford Health Care and other local health care providers to make extremely difficult decisions to close or reduce programs, deeply affecting the availability of care locally.

Q: What would be the impact of Measure F on Stanford's neighbors in Palo Alto?

Livingston: First is the impact on care. We are proud of the role that Stanford Health Care plays in providing local communities with the peace of mind that comes from accessible, top-quality health care close to home. Measure F stands to jeopardize that — not just for Stanford Health Care, but also for Palo Alto Medical Foundation and other clinics and hospitals, even local dentists and eye doctors. But it wouldn't just severely limit access to care.

Measure F would also place a tremendous financial and administrative burden on the City of Palo Alto. The City Council voted unanimously to oppose it. Mayor Liz Kniss, who is also a nurse, signed a letter with other health care professionals that said Measure F would fail to improve health care in the city — yet, at the same time, it would force the city to raise taxes, reduce city services and/or lay off employees. That's a lose-lose proposition for everyone.

Q: People in the Stanford community may have heard radio ads criticizing the infection rates at Stanford Health Care. What should the university community know about this?

Hawn: SEIU-UHW has spent nearly a million dollars on a series of ads to attack our patient care and quality. These ads unfairly criticize our employees and their hard work by using outdated data.

(From left) David Entwistle, Mary Hawn and Randy Livingston.

For example, one ad cherry-picks a rate for C. difficile infections from 2014 that doesn't represent our current, much improved outcomes. In fact, that rate dropped by 45 percent between fiscal years 2014 and 2018 to date. In the last fiscal year alone, hospital-acquired infections decreased by 30 percent, and length of stay decreased by 12 percent.

Hospital-acquired infections and other quality issues are a challenge across the health care system, particularly for academic medical centers, whose patient populations contain many more complex cases where infection is a substantially higher risk. Today, we have over 120 unique safety and quality initiatives incorporating the expertise of clinicians, patients and infection control physicians. Our online resource, www.StanfordHealthCareQuality.com, has more information about our record and commitment to patient safety.

Q: What is Stanford's approach to infections and patient safety?

Hawn: As an academic medical center, Stanford Health Care provides care for some of the sickest patients in the world. These very ill patients with complex conditions are particularly prone to health care-associated infections due to their frailty and vulnerability, and we continually seek to protect them by improving our already excellent infection control.

At Stanford Health Care, patient care as well as patient support departments and services participate in comprehensive infection reduction and prevention programs. Hospital committees and task forces focus on decreasing hospital-acquired infections such as central line-associated bloodstream infections, catheter-associated urinary tract infections, and C. difficile infections. Efforts also include focused surveillance, such as identification and tracking of hospital-acquired infections, compliance with process measures and monitoring for necessary corrective actions.

Despite receiving some of the sickest patients, we maintain very positive outcomes — even compared to hospitals that treat patients with less severe illnesses. This is because we go to extraordinary lengths to provide safe, clean environments. And we continue to make great strides when it comes to infection prevention and control efforts. ISM

Stanford University statement opposing Measure F in Palo Alto

Stanford University opposes Measure F, an initiative on the November ballot in the City of Palo Alto, because it would threaten Stanford Health Care's ability to provide top-quality health care to patients from Palo Alto and across the region.

Supported by the research engine of Stanford University, Stanford Health Care is one of the nation's leading health care providers and is committed to providing the highest quality care to patients from Palo Alto, the Bay Area and around the world. As an academic medical center, Stanford Health Care often serves critically ill patients with complex medical needs. It receives more than 680,000 ambulatory visits and 53,000 emergency room visits annually, and offers the only level-1 trauma center between San Francisco and San Jose.

Measure F proposes to limit charges to commercially insured patients at Stanford Health Care — as well as at Palo Alto Medical Foundation, Kaiser Permanente affiliates and other health care providers in the city — to no more than 15 percent above the "reasonable cost" of providing "direct" patient care. Such a policy is estimated to reduce Stanford Health Care's budget by 25 percent, requiring significant cutbacks and the possible closure of many services and programs that are essential to high-quality health care in the local area.

The proposal generally would not affect what patients actually are charged for services, but rather would force Stanford Health Care to pay any rebates to insurance companies. Meanwhile, it would prevent Stanford Health Care from being paid for managers, technology and administrative expenses, and hospital services required by state law.

Measure F also would require the City of Palo Alto to create a costly new regulatory structure to enforce the new regulations.

Stanford also opposes Measure U, a similar measure in the City of Livermore, where Stanford Health Care operates ValleyCare Medical Center.

The university typically does not take positions on external political issues unless they directly impact its mission. These measures do. The patient care provided by Stanford Health Care is an integral part of Stanford University's mission and is a major part of the university's contribution to the health and quality of life of our region. As with any election issue, the university encourages individual members of the university community to review the facts of the issue and cast an informed vote, whatever their final judgment on the merits of the issue. ISM

Eight scientists awarded NIH grants for high-risk, high-reward research

Eight School of Medicine researchers have been awarded High-Risk, High-Reward Research grants from the National Institutes of Health.

In all, the Stanford researchers will receive $32 million over the next five years to fund their investigations. The grants support high-risk research efforts with the potential to make a big impact in the biomedical sciences. This year, the NIH gave 89 awards totaling $282 million.

"We're honored that the NIH has recognized the promise of the endeavors proposed by these gifted Stanford scientists," said Lloyd Minor, MD, dean of the School of Medicine. "By stretching the limits of our biomedical understanding, our researchers are helping to realize Stanford Medicine's goal of making health care more precise, predictive and proactive."

Two of the Stanford scientists received Pioneer Awards, two received New Innovator Awards and four received Transformative Research Awards. The grant program is part of the NIH Common Fund.

PIONEER AWARD

The Pioneer Award provides up to $3.5 million, dispensed over five years, to investigators at all career levels to pursue new research directions and develop groundbreaking, high-impact approaches to a broad area of biomedical or behavioral science.

Christina Curtis, PhD, assistant professor of medicine and of genetics, plans to use her award to study how human tumors develop and to predict their progression. Her research focuses on understanding cancer systems biology, or the complex way in which many aspects of biology interact in healthy and diseased states. Akin to weather forecasting, the goal is to ultimately allow clinicians to anticipate how a tumor will behave over time, as well as to steer its course and tailor treatment options.

Christina Curtis

"Characterizing how a patient's tumor changes over time, adapts to therapy and sometimes spreads to other tissues is challenging since this process often cannot be directly measured," Curtis said. "Yet, learning cancer's evolutionary rulebook will give us clues about a patient's prognosis and is a necessary step toward the development of predictive models."

To overcome these challenges, Curtis has developed powerful computational and statistical techniques to infer an evolutionary history of tumors by analyzing the patterns of mutations present in their genomes and comparing these with virtual tumors simulated under different scenarios. She is also working to measure tumor adaptation during development and tumor progression in real time by leveraging new methods to trace cell lineages.

Curtis is co-director of the Stanford Molecular Tumor Board and a member of the Stanford Cancer Institute, the Canary Center at Stanford for Cancer Early Detection and Stanford BioX.

Michelle Monje, MD, PhD, associate professor of neurology and neurological sciences, studies a group of deadly brain tumors called high-grade gliomas. Monje's team recently discovered that gliomas grow in response to nervous system activity, and that the cancer cells depend on signals from healthy neurons to develop.

Michelle Monje

Monje's award will enable her to expand the tactics her team uses for studying how glioma cells form functional circuits with healthy brain cells: In studies of mice implanted with human gliomas, she plans to employ optogenetics, calcium imaging and measurements of membrane depolarization to map, monitor and control the circuit dynamics of high-grade gliomas as the disease evolves.

"With this award, I'll be building my lab's electrophysiology and in vivo imaging capabilities to get a global view of how gliomas integrate into neural circuitry," she said. "We hope to identify specific patterns of glioma circuit activity that could be therapeutically modified to give better outcomes for these intractable cancers."

Monje is also a pediatric neuro-oncologist at Lucile Packard Children's Hospital Stanford and a member of Stanford Bio-X, the Stanford Child Health Research Institute, the Stanford Institute for Stem Cell Biology and Regenerative Medicine, the Stanford Cancer Institute and the Stanford Neurosciences Institute.

NEW INNOVATOR AWARD

Alistair Boettiger, PhD, assistant professor of developmental biology, received a New Innovator Award, which provides up to $1.5 million over five years to fund innovative research by investigators who are within 10 years of their final degree or clinical residency and who have not yet received a research project grant or the equivalent from the NIH.

Boettiger's research explores how genomes fold within a cell's nucleus to affect gene expression.

"Like a book printed on origami, in which folding the pages changes the course of the story, the genomes of higher animals fold to connect or conceal different parts of this genetic blueprint to control cell behavior," Boettiger said. "My lab is developing new microscopy approaches to observe this folding with detail never before achieved. This award will help us focus this technology on the developing embryos of diverse animal species to better understand the conserved mechanisms that shape genome organization and contribute to cell differentiation. It will also allow us to tap new genome-editing approaches to determine which sequences direct folding decisions."

Alistair Boettiger

The ability to read and understand the distinct three-dimensional blueprints of a single cell will enable researchers to discern the links between an organism's genome sequence, individual traits and the genetic aspects of health.

Boettiger is a National Academy of Sciences Kavli Fellow, a Beckman Young Investigator and a member of Stanford Bio-X.

Manish Saggar, PhD, assistant professor of psychiatry and behavioral sciences and director of the Brain Dynamics Lab at Stanford, focuses his research on developing computational methods to better understand how the human brain adapts from doing one thing to the next, both in people who have mental health problems and those who don't.

He intends to use his New Innovator Award to develop a computational framework for modeling how an individual's brain activity changes over time.

Manish Saggar

"I propose to take already collected neuroimaging data from individuals who are diagnosed with either major depression or ADHD and use these new modeling techniques to capture clinically meaningful insights about changes in the brain's intrinsic activity without averaging data across space, time or individuals," Saggar said.

This new computational framework could both be used for developing biologically grounded stratification of mental illnesses and as a test bed for developing future treatments and personalized care for patients, he said.

Saggar is a member of Stanford Bio-X, the Stanford Child Health Research Institute and the Stanford Neurosciences Institute.

TRANSFORMATIVE RESEARCH AWARD

The award supports individuals or teams proposing projects that are inherently risky and untested, but that have the potential to create new paradigms and may require large budgets.

Karl Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavior sciences and the D.H. Chen Professor, and **Anne Brunet**, PhD, professor of genetics and the Michele and Timothy Barakett Endowed Professor, will use their five-year, $13.75 million award to advance the basic science of how the brain and the aging process control each other.

Karl Deisseroth

They intend to develop new technologies for collecting brain-wide, neuronal activity signals at cellular resolution across the entire life span of a vertebrate animal from the beginning of its life until its death.

"We expect these new technologies and follow-on basic science discoveries to be directly pertinent to major societal problems facing the United States and the world," said Deisseroth, whose research focuses on developing molecular and cellular tools to observe, perturb and re-engineer brain circuits. "Aging leads to a decline in cognitive abilities, even in healthy individuals, and is the leading risk factor for conditions such as Alzheimer's disease. Meanwhile, the median age of the human population continues to rise on all continents."

Anne Brunet

Brunet's work concerns the molecular mechanisms of aging and longevity, with a particular emphasis on the nervous system. "We're looking to identify ways to observe changes in the brain during aging," she said. "We've pioneered genetic and genome-editing tools to transform a short-lived vertebrate, the African killifish, into a premier model organism for studying aging and age-related diseases such as Alzheimer's disease. We feel that this system is ideally suited to discover new neuronal networks that respond to aging and can regulate its pace."

Deisseroth and Brunet are members of Stanford Bio-X and the Stanford Neurosciences Institute. Additionally, Brunet is a member of the Stanford Cancer Institute and the Stanford Cardiovascular Institute and co-director of the Stanford Glenn Center for the Biology of Aging. Deisseroth co-directs the Stanford "Cracking the Neural Code" program and is a Howard Hughes Medical Institute investigator.

Roger Kornberg, PhD, professor of structural biology and the Mrs. George A. Winzer Professor in Medicine, won the 2007 Nobel Prize in chemistry for his pivotal research into the transcription process by which genetic information residing on chromosomal DNA is copied in the form of mobile molecules of RNA. He plans to use his five-year, $7.5 million award to focus on chromosomal structure at a high level of resolution.

Roger Kornberg

"The 3-D structure of chromosomes is the richest unexplored territory in cell science," Kornberg said. "Chromosomes are large, dynamic, complex and fundamental, underlying cell differentiation, cell physiology and disease. They are also enigmatic, exhibiting at the same time structural heterogeneity and order, physical flexibility and rigidity, and functional activity and silencing."

He intends to probe and dispel these mysteries by determining chromosome structure at 10- to 20-nanometer resolution. "Our approach is applicable to chromosomes in all physiologic states, at all stages of the cell division cycle," he said.

Kornberg is a member of Stanford Bio-X.

Alice Ting, PhD, professor of genetics and of biology, develops technologies to map out cells and delineate the signals and circuits that give rise to cell function. Ting's research harnesses a variety of molecular approaches and protein-engineering tactics to detect, measure and manipulate specific molecules that could play crucial roles in cell and animal behavior.

Ting and her collaborators at MIT, Harvard and the University of Southern California have received a Transformative Research Award for a project that seeks to understand how different organ systems communicate with one another to affect each other's functions. The scientists aim to decipher the exact molecules that traverse multiple organ systems to facilitate "cross-talk," and understand how one tissue might influence another. To tag and track molecules of interest in the body, the group will use an enzyme called TurboID, which Ting created in her lab in the fall of 2017.

Alice Ting

TurboID carries a special marker engineered to stick to the molecules in its immediate proximity.

"The idea is, tag a wide range of molecules found in a single type of tissue, such as fat, and subsequently look for those tagged molecules in a different tissue, such as muscle," Ting said. Those with the tag will have come from the fat and can be further investigated to understand any functional significance. The grant totals more than $8 million, of which about $637,000 will be funneled directly to Stanford to support Ting's continuing efforts to develop and refine the TurboID enzyme and proximity-labeling technology. Ting is a member of Stanford Bio-X, the Stanford Child Health Research Institute, Stanford Cancer Institute, Stanford ChEM-H and Stanford Neurosciences Institute. **ISM**

Chan Zuckerberg Biohub funds new research efforts, initiative

By Amy Adams

Thirteen Stanford faculty are among the leaders of six research teams that received funding from the Chan Zuckerberg Biohub. Combined with the new microbiome initiative, which includes four Stanford faculty, the CZ Biohub is committing $13.7 million over three years to new collaborative research to enhance human health.

The intercampus research awards were given to teams of investigators that include faculty from Stanford, UCSF and UC-Berkeley with the goal of fostering scientific research collaboration across the Bay Area.

"This new collaborative, team-based funding allows investigators across the three campuses to tackle demanding problems to enhance health," said Stephen Quake, PhD, co-president of the CZ Biohub and professor of bioengineering and of applied physics at Stanford. "These research teams will shed new light on a diverse and challenging set of questions that will advance our understanding while developing technologies that open fresh avenues of research."

Steven Palumbi, PhD, professor of biology, is one of five leaders on a team that received funding to investigate genome evolution and cell biology in organisms that aren't traditional laboratory animals. "Mice can't regenerate limbs, but we study worms that can, and corals can live thousands of years," he said. "There are amazing things that these organisms do regularly that reveal the limits of our own cell biology."

The CZ Biohub also announced funding to expand on the microbiome initiative that launched as a pilot program earlier this year. That initiative will carry out research on the community of microbes within the human body that influence many aspects of health, from nutrition and immune function to drug metabolism.

Of the eight investigators leading the initiative, four are Stanford faculty: Michael Fischbach, PhD, associate professor of bioengineering; KC Huang, PhD, associate professor of bioengineering and of microbiology and immunology; David Relman, MD, professor of medicine and of microbiology and immunology; and Justin Sonnenburg, PhD, associate professor of microbiology and immunology.

"The human microbiome is incredibly complex, individual and dynamic," Sonnenberg said. "Hundreds of microbial species are a fundamental part of human biology, contributing to health and in some cases causing disease, so this is an important but difficult set of biomedical problems to address."

"These research teams will shed new light on a diverse and challenging set of questions."

As part of the microbiome initiative, CZ Biohub will establish a mass spectrometry facility for metabolomics at Stanford. The Biohub plans to make unused instrument time available to other members of the research community. It's also exploring the idea of making software tools, mentoring and training accessible to biologists and engineers who are not specialists in metabolomics.

The CZ Biohub encourages collaboration between Bay Area institutions with regular meetings and chances for their investigators to exchange ideas. Team leaders of the intercampus research awards will be expected to participate in at least half of the biweekly meetings and to upload manuscripts reporting work supported by these awards to preprint servers such as bioRxiv.org or arXiv.org to accelerate the pace of scientific discovery.

The six awards and team leaders are:

Beyond model systems: Insights into genome evolution and cellular innovations — Christopher Lowe, Stephen Palumbi and Irving Weissman, Stanford; Daniel Rokhsar, UC-Berkeley; Wallace Marshall, UCSF.

Social network analysis of neuroimmune interactions in the developing human brain — James Zou and Alice Ting, Stanford; Tomasz Nowakowski, Jimmie Ye and Alex Pollen, UCSF; David Schaffer, UC-Berkeley.

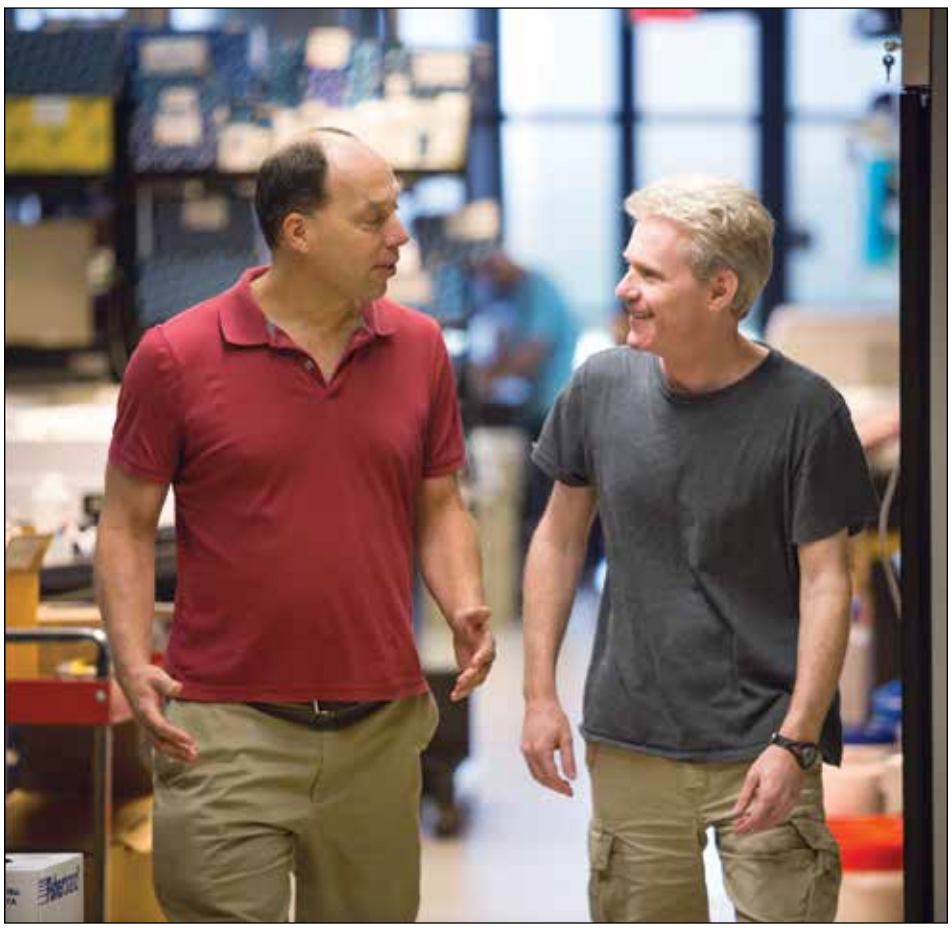
Multi-scale deep learning and single-cell models of cardiovascular health — Euan Ashley and James Priest, Stanford; Rima Arnaout and Atul Butte, UCSF; Ben Brown and Bin Yu, UC-Berkeley.

Machine learning for interpreting rare genetic variation in comprehensive newborn screening and pharmacogenetics — Russ Altman and Carlos Bustamante, Stanford; Steven Brenner and Michael Jordan, UC-Berkeley; Renata Gallagher and Kathleen Giacomini, UCSF.

Defining host responses of virus-infected and uninfected neighbor cells — Karla Kirkegaard and Peter Sarnow, Stanford; Laurent Coscoy, UC-Berkeley; Melanie Ott, UCSF, Gladstone Institutes.

Imaging complex biological machines in action — Wah Chiu and John Boothroyd, Stanford; Carolyn Larabell, UCSF; James Sethian, UC-Berkeley. **ISM**

TYLER MALLORY



Stanford's Stephen Quake (left) and UCSF's Joseph DeRisi lead the Chan Zuckerberg Biohub.

Add your 'voice' to Stanford Hospital mosaic project

The Stanford Medicine community and local residents are invited to participate in a digital mosaic project to celebrate the opening of the new Stanford Hospital in 2019.

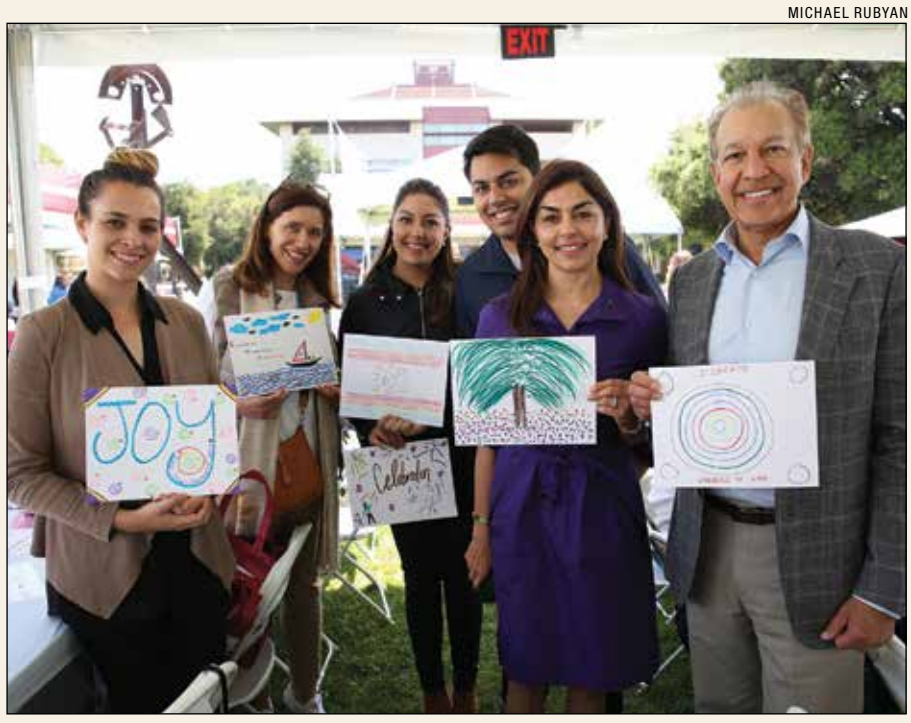
Thousands of drawings are being collected through January for the "Voices of the Community" project and will be assembled into a digital mosaic that will depict the new hospital. Participants can also attend one of several collection events this fall, or sign up to host an interactive collection at, for example, their school, club or block party.

The next collection event on campus will be Oct. 14 at the Stanford Cantor Arts Center's Second Sunday Family Program. The collection will take place from 11 a.m. to 2 p.m.

Those who aren't able to attend the collection events can drop off their art submissions at the Stanford Health Library's main branch in the Hoover Pavilion, at 211 Quarry Road in Palo Alto, during business hours.

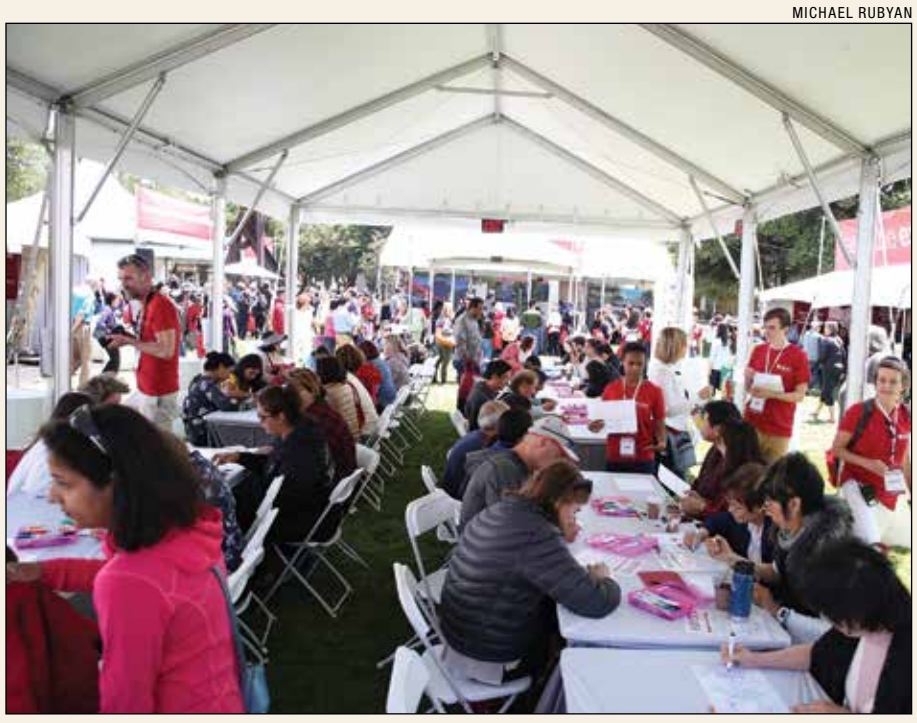
Artwork can also be submitted through the project's website at voices.stanford.edu. **ISM**

MICHAEL RUBYAN



Local families shared their creativity and excitement about the opening of the new hospital at a recent art collection event.

MICHAEL RUBYAN



People who attended this year's Health Matters event had the opportunity to create drawings in the "Voices of the Community" tent.

Ceremony

continued from page 1

lutionizing itself, and it's going to be immensely more interesting than you can even anticipate now, sitting in the seats where you are," Bilder said.

Exhorting the incoming class to uphold the highest values of the scientific community, Bilder also told them "to work to expand this community, to promote opportunity and diversity within it, and to break down these really absurd ideas, traditional ideas, about who can or who cannot be a scientist." He called on students to "seize this chance to do ambitious, risky and transformative research," assuring them that "until you succeed, your community is here to sustain you."

Sitting directly in front of her mother Katie Arnoldi, who had flown in from Southern California to cheer her on, incoming biology student Natalie Arnoldi was excited to start a new chapter at Stanford. Arnoldi, who in 2014 received both a bachelor's degree in marine biology and master's degree in oceanography and marine policy from Stanford, had spent her last four years pursuing her art career and showing her large oil paintings internationally.

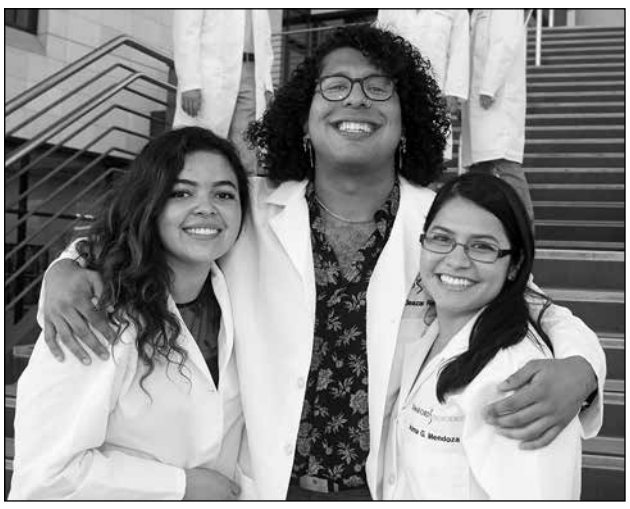
"My dream is to mesh the two," Arnoldi said. "It's a myth that you have to choose between art and science. You can have it all."

As students were introduced by their department chairs, they proceeded across the stage to be assisted into their lab coats by Talbot and Hope. Their classmates and loved ones in the audience applauded and shouted, and some held up handmade signs of support.

Naomi Lynn Haddock, who grew up in Honduras and Indiana, said she had always been "a bit star-struck about Stanford," and worked hard to get here. Haddock said her white lab coat was "something tangible that shows I'm really here." She said she was proud to be the first on the Honduran side of her family to attend graduate school, and that she plans to study infectious disease immunology and hopes to become a professor and serve as a mentor.

Renteria, the first in his family to attend college, said he wants to help others aspiring to study science. "Receiving my white coat represents an inflection point of sorts, in the sense that many people contributed to my ability to get here, and I'm reaching a point where I can start to figure out how to give back so others can reach their full potential as well," he said. "I may not have my PhD yet, but I think I'm in a privileged position at Stanford to help others." **ISM**

GEORGE NIKITIN



(Clockwise from above) First-year graduate students in the biosciences wear their new lab coats following the PhD lab coat ceremony on Sept. 24 at the Li Ka Shing Center for Learning and Knowledge. Students before the ceremony in the center's Berg Hall. Students (from left) Naomi Haddock, Andy Renteria and Alma Mendoza.

Pond-dwelling microbes swim in polygons to avoid increased light

By Amy Adams

In any seemingly quiet pond, the still waters actually teem with tiny pond dwellers called Euglena gracilis. Unseen to the naked eye, the single-celled organism spirals through the water, pulled along a relatively straight path by a whiplike appendage, in search of just the right level of light.

But Stanford researchers have discovered how, under some circumstances, Euglena halts its forward progress and begins tracing out elaborate counterclockwise polygons — triangles, squares, pentagons — in a mathematically defined effort to find a better environment.

The discovery, described in a paper published Sept. 24 in *Nature Physics*, could help scientists design tiny swimming robots of the future to be more efficient and effective at maneuvering through the bloodstream, for example, or navigating watery environments.

"We're trying to understand biological systems in a mathematical way," said Ingmar Riedel-Kruse, senior author of the paper and assistant professor of bioengineering. "Seemingly simple feedback loops in single cells can actually generate rather complex behaviors in order to accomplish various tasks."

Well-studied organism

Scientists in the 1800s once marveled at finding Euglena — a greenish oblong with a red eyespot and long, whiplike flagellum for swimming — under a microscope. Since then, the organism has been observed by countless generations of biology students. With such a history of being watched, it came as a surprise when postdoctoral scholar Alan Tsang, PhD, the study's lead author, observed Euglena's behavior in a computer model he'd developed to study how it moves in relation to light. In his model, when he simulated increased light, the organism began tracing out polygons.

Riedel-Kruse remembered being skeptical when Tsang first described what his model predicted.

"It was hard to believe that it's true," Riedel-Kruse said. "I thought there was something wrong with the code." But when the pair checked under the microscope — increasing light levels as in the simulation — there were the polygons.

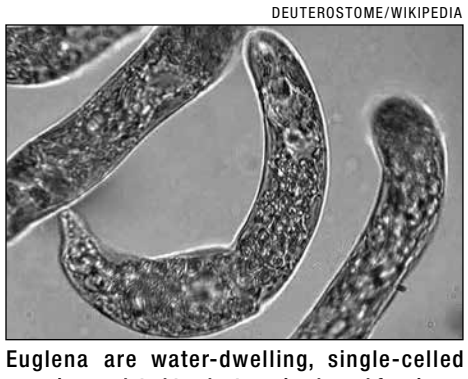
The shapes are a result of how Euglena navigates the world. Because the organism normally rolls through the water on its long axis, the eyespot rotates to survey 360 degrees of light. In steady light conditions — which are normal under a microscope — it meanders along in a relatively straight path.

However, Tsang said, if the eyespot detects increased light intensity, the Euglena makes a hard turn. "Then they don't see the light and they swim straight again," Riedel-Kruse said. "But since they keep rolling, then after a full cycle they see again the strong light so they make another strong side turn."

Enough straight lines followed by sharp turns, and a triangle is born.

Tsang noticed that over the course of about 30 seconds, Euglena adapted to the stronger light and the turns became less sharp, creating ever-expanding polygons — squares, then pentagons — until, finally, the Euglena headed in a relatively straight line.

DEUTEROSTOME/WIKIPEDIA



Euglena are water-dwelling, single-celled organisms related to plants, animals and fungi.

As for why nobody had seen this before, Riedel-Kruse said people rarely alter light levels while observing Euglena under a microscope. But since Tsang was specifically trying to model how the organism moves in relation to light, the behavior appeared.

A sensible behavior

Riedel-Kruse argued that the behavior makes sense for a Euglena swimming along in a pond under a comfortable source of shade. When it suddenly encounters bright sunlight, it can turn quickly to seek a patch of shade. By slowly spiraling outward if the first few turns didn't work, the Euglena ups its chances of eventually getting out of the sunlight.

Riedel-Kruse's lab studies Euglena in part to better understand how microorganisms navigate their watery worlds. The researchers also integrate what they learn about Euglena into interactive biology setups for education. Euglena is an unusual organism that can both make its own food and eat what it finds in the water. It is related to plants, animals and fungi — all known as eukaryotes — but is a separate group with some unique characteristics.

"Because it is part of an outgroup to most eukaryotic life, you could learn something that is general, and you can also find out how diverse eukaryotic life can be," Riedel-Kruse said. "That makes Euglena really interesting to me."

What's more, Riedel-Kruse and Tsang said what they learn — and the mathematical models they developed — could be useful for microscale robotics.

"There is an emerging field where people are trying to engineer and program microscopic swarm robotics for things like microsurgery or drug delivery," Tsang said. "I definitely see people looking for efficient control mechanisms at the microscale."

Postdoctoral scholar Amy Lam, PhD, also co-authored the study, which was supported by the National Science Foundation, the Stanford Discovery Innovation Fund and the Croucher Foundation.

Stanford's Department of Bioengineering, which is jointly managed by the schools of Medicine and of Engineering, also supported the work. **ISM**

Toy

continued from page 1

management and policy and of industrial and operations engineering at the University of Michigan. "Usually, you need to be able to work with experts in many different countries."

Hooked on mathematical modeling

Her parents are Turkish and raised Toy and her sister in the Netherlands. In addition to Dutch and Turkish, she speaks English, German and some French. Being multilingual has come in handy in her work with the World Health Organization. "It helps to have a multicultural background," she said. "You need to be able to adapt easily to conditions and the people within the areas where you're working."

Toy initially studied epidemiology, the branch of medicine focused on the prevalence and distribution of disease. But one of her professors got her hooked on mathematical modeling. She earned a PhD in public health at Erasmus University Medical Center in Rotterdam and became a decision scientist.

"A decision scientist helps to pick up loose ends when decisions have to be made. They consider, among other things, the costs associated with various alternatives," Toy said. "For instance, when faced with cancer treatment alternatives, what is the best alternative for the population and the person?"

As a graduate student, Toy looked at the public health impact of antiviral therapy for hepatitis B. Her work resulted in public health policy changes in the Netherlands and in Turkey. After completing her PhD, Toy accepted a fellowship at Harvard to study international health and spent a good deal of time in China doing research. She focused on several cost-effective interventions for chronic hepatitis B infection and became a recognized expert, publishing her work in prominent journals. China also enacted health policy changes because of Toy's work, which provided policymakers the evidence they needed to procure low-cost drugs for a national viral hepatitis treatment program.

'What if?'

To build her cost-effectiveness models, Toy starts with figuring out how many lives can be saved with a particular treatment, and then she plays with variables contributing to costs to see under what conditions the treatment will be cost-effective or cost-saving. She does this by asking, "What if?" If there is a 10 percent prevalence rate of a disease, but most of it is seen in adult males, what if 90 percent of those men were screened for the disease? What if 80 percent of those who had the disease got treated? She said she always has to think of the future to include factors that may not be relevant now. A cure might be within reach, or bioindustry costs may change, or the political climate could impact a number of variables, she said.

One of the biggest challenges of being a decision scientist is getting access to the specific data sets needed to build a particular model, Toy said. "Sometimes physicians or researchers or drug companies just don't want to share data with you," she said. Now that she has established herself as a leader in the field, it's easier to develop collaborations.

STEVE FISCH

A decision scientist, Toy came to Stanford in 2013 to work with Samuel So, executive director of the Asian Liver Center.

Toy came to Stanford in 2013 as a postdoctoral scholar to work with Samuel So, MD, executive director of the Asian Liver Center, which seeks to address the disproportionately high prevalence of chronic hepatitis B and liver cancer in Asians and Asian-Americans. Toy traveled to the Philippines, Mongolia, Indonesia and Australia, among other places, to contribute to the center's outreach efforts and to gather information for WHO.

The best part about being a decision scientist, Toy said, is being able to create user-friendly tools that health ministries can use to inform decisions affecting health policy. She built a model in a spreadsheet that was made freely available to health ministries and is now available online. She recently gave a two-day workshop in Indonesia to teach health care leaders how to use it and how to enter and adjust variable amounts to lower the cost of health care. "It also serves as an outreach tool," she said. "By emphasizing that hepatitis B is a serious disease, this sort of outreach can impact health policy."

Basis of a national strategy

Toy was commissioned by the National Academies of Sciences, Engineering and Medicine to model the potential impact of improving chronic hepatitis B patient care and treatment in the United States. "I was very humbled that I could be asked to do such a thing," she said. "It made me very happy and proud to be calling the U.S. my home. It really made me feel like I was at home." Her study, published in March of 2017, concluded that it was feasible to eliminate the public health problem of hepatitis B in the country by 2030 and formed the basis of a national strategy that changed health care policy in the United States.

She was invited by the Centers for Disease Control and Prevention to present her hepatitis B model the following month at the viral hepatitis summit in Atlanta. Her colleagues praised her ability to make such a complicated model easy to understand in the presentation. The conference was streamed live. Her family and friends were thrilled to be able to watch from over 4,000 miles away. "They took so many screenshots!" Toy said.

Looking to the future, Toy is interested in expanding her work to have a broader reach and developing applications that haven't been explored yet. She's working on a prediction model of liver cancer for patients to use. Nothing like that is currently available.

"By entering basic data such as age, gender and blood test results, the tool will calculate the probability of liver cancer in a given amount of time and can potentially guide the patient to follow recommended monitoring and treatment," Toy said. "We need simplified tools to communicate complex information to patients."

It will be a collaborative effort, drawing on the expertise of clinical psychologists, user-experience designers, biomedical informaticists and decision scientists. "This is using public outreach on an individual level to affect patient outcomes," Toy said. "Putting these powerful tools in the hands of patients has the potential to make a huge impact on behavior change."

Does Toy use decision models in her personal life? When she was in Boston, she used modeling for decision-making in life just for fun with a few colleagues, she said. "We would try to answer a question in our personal life and give weights/utilities to some of these states to predict an outcome." She doesn't do that anymore but does apply the pragmatic part of modeling to her life. "I used to be more spontaneous with decision-making, but lately I am trying to take my time," she said. **ISM**

Varicose

continued from page 1

and varicose veins and may provide clues for treating the condition," said Nicholas Leeper, MD, associate professor of surgery and of cardiovascular medicine at Stanford.

The study also identified 30 genes linked to varicose vein disorder and to a strong genetic correlation with deep vein thrombosis. It was published Sept. 24 in *Circulation*. Leeper and Erik Ingelsson MD, PhD, professor of cardiovascular medicine, are the senior authors. Eri Fukaya, MD, PhD, clinical assistant professor of vascular surgery, and medical student Alyssa Flores share lead authorship.

Varicose veins are swollen, twisted veins that can be seen just under the surface of the skin, usually in the legs. More than 30 million people in the United States have varicose veins. Although the condition is often dismissed as nothing more than a cosmetic nuisance, it can cause moderate pain and has been linked to the more serious side effects of deep vein thrombosis, which occurs when a blood clot forms in one or more of the deep veins in the body.

'Shockingly little is known'

"The condition is incredibly prevalent but shockingly little is known about the biology," Flores said. "There are no medical therapies that can prevent it or reverse it once it's there." Treatment is mainly limited to surgical procedures, such as laser treatment or vein stripping. "We're hoping that with this new information, we can create new therapies, as our study highlights several genes that may represent new translational targets," she said.

Researchers used data from the UK Biobank — both a long-term study and genetic repository that includes genomic data on about a half-million people — to look for varicose vein risk factors using machine learning combined with epidemiological methods in 413,519 participants. Further, they screened for genetic markers using genomewide association studies in 337,536 of the participants, 9,577 of whom had varicose vein disease. The study confirmed that currently established risk factors — including being older, female, overweight or pregnant, or having a history of deep vein thrombosis — all are associated with varicose veins.

"We confirmed that having had deep vein thrombosis in the past puts you at increased risk in the future," Leeper said. "Recent research suggests that the converse appears to be true as well. Having varicose veins puts you at risk of these blood clots."

The study also confirmed that surgery on the legs, family history, lack of movement, smoking and hormone therapy are risk factors. But the correlation they found between height and the condition was unexpected, the researchers said.

"We were very surprised to find that height came up from our machine-learning analyses," Flores said.

Turning the algorithm loose

Nicholas Leeper

Typically in a large, genetic study like this one, researchers use genomewide association studies to examine DNA variation that may be associated with an increased risk for a particular illness. Using this method, the researchers identified the 30 regions on the genome associated with varicose veins. But the researchers also used another method involving machine learning, a type of artificial intelligence, to cast a giant net to discover any previously unknown risk factors.

"These methods represent new ways of thinking about research," Ingelsson said. "You go in without a hypothesis about a specific biological mechanism and scan for something new. You could say that you turn the machine loose on it. In this case, we included 2,716 predictors of varicose veins in this machine-learning algorithm. Then we let the algorithm find the strongest predictors of varicose veins."

> "Our results strongly suggest height is a cause, not just a correlated factor."

In addition to height, the machine-learning algorithm showed that bioimpedance, a measure of how well the body impedes electric current flow, is a strong predictive marker for varicose veins. This measurement could potentially be used as a diagnostic tool to predict for varicose veins, Leeper said.

When height emerged from the machine-learning analysis as a possible risk factor, the researchers conducted further tests to see if it was an actual cause for the disease using mendelian randomization analyses, a statistical technique to determine causal effects.

"Our results strongly suggest height is a cause, not just a correlated factor, but an underlying mechanism leading to varicose veins," Ingelsson said.

He added, "By conducting the largest genetic study ever performed for varicose vein disease, we now have a much better understanding of the biology that is altered in people at risk for the disease."

Daniela Zanetti, PhD, a postdoctoral scholar at Stanford, also contributed to the study, as did researchers at Uppsala University in Sweden.

The study was supported by funding from the National Institutes of Health and the Knut and Alice Wallenberg Foundation.

Stanford's Department of Medicine also supported the work. **ISM**

Steven Artandi tapped to lead Stanford Cancer Institute

By Krista Conger

Steven Artandi, MD, PhD, professor of medicine and of biochemistry at the School of Medicine, has been named the new director of the Stanford Cancer Institute, effective Oct. 1.

Artandi replaces Beverly Mitchell, MD, who has served as director for the past 10 years. Mitchell, a professor of medicine, will continue her involvement with the institute as senior adviser, researcher and mentor.

"A strategic thinker and collaborative physician-scientist, Dr. Artandi's understanding of the opportunities to develop synergies between the elements of our tripartite mission — excellence in research, patient care and education — make him uniquely qualified to further the SCI's goal of translating Stanford discoveries into individualized cancer care," said Lloyd Minor, MD, dean of the School of Medicine. "His work is already producing new insights into the origins of cancer, revealing how aspiring cancers circumvent critical bottlenecks encountered during carcinogenesis, and leading to new therapies with the potential to treat many of the most refractory human cancers."

Artandi, who holds the Jerome and Daisy Low Gilbert Professorship, is a cancer biologist whose research focuses on the role played by the enzyme telomerase in cancer, aging and stem cell biology.

Steven Artandi

"I'm very honored to be the next director of the Stanford Cancer Institute, particularly at this exciting juncture in the history of cancer research and cancer therapy," Artandi said. "We are entering a period during which major translational discoveries will transform our approach to treating cancer patients. Stanford has remarkable strengths in innovation, basic science, clinical medicine and translation. We're also fortunate to have extraordinary people, including faculty, trainees, nurses and staff. At SCI, we're uniquely positioned to drive forward the next wave of discoveries to benefit our cancer patients."

Artandi came to Stanford in 2000 after completing a fellowship in medical oncology at the Dana Farber Cancer Institute and Massachusetts General Hospital. In 2015, he received an outstanding investigator award from the National Cancer Institute. He earned his MD and PhD in microbiology in 1995 from Columbia University.

"Dr. Artandi is a highly accomplished physician-scientist who will take the Stanford Cancer Institute to the next level," said Mary Hawn, MD, professor and chair of surgery at Stanford. "He has innovative plans to translate science to patients that will markedly impact care."

Hawn and Thomas Montine, MD, PhD, professor and chair of pathology, co-chaired the search committee for the new director.

"We are delighted to have Dr. Artandi as the next director for the Stanford Cancer Institute," Montine said. "His leadership will doubtless help the institute continue to improve outcomes for patients facing cancer diagnosis and treatment." ISM

OF NOTE

reports on significant honors and awards for faculty, staff and students

Yiyin Chen

Karlene Cimprich

Jennifer Cochran

Daniel Ennis

Juan Fernandez-Miranda

Kimberly Kopecky

Michelle Monje

Lori Muffly

Michelle Odden

Matthew Wheeler

YIYIN CHEN, MD, PhD, a postdoctoral scholar in bioengineering, was named a Howard Hughes Medical Institute Hanna H. Gray Fellow. The fellows program, which seeks to increase diversity in the biomedical research community, will provide Chen with as much as $1.4 million in funding over eight years. She will study how a microbe's context — its genetic makeup and the microbes nearby — influences its potential for maintaining health or causing inflammation.

KARLENE CIMPRICH, PhD, professor of chemical and systems biology, received a research professor award from the American Cancer Society. The five-year award provides $80,000 per year to researchers who have a proven history of pioneering, influential cancer research and mentorship. Her research focuses on understanding how cells maintain genomic stability, with an emphasis on how they respond to DNA damage and the stress of replication.

JENNIFER COCHRAN, PhD, was promoted to professor of bioengineering, effective Aug. 1. She is the chair of the Department of Bioengineering. Her research focuses on developing technology for high-throughput protein analysis and protein engineering, and on discovering molecules that could become drugs for use in ophthalmology, cardiovascular disease, neurodegeneration and cancer therapy.

DANIEL ENNIS, PhD, was appointed associate professor of radiology, effective Aug. 1. He directs radiology research at the Veterans Affairs Palo Alto Health Care System. His research interests include the basic science and clinical applications of MRI for evaluating cardiovascular structure, function, blood flow and remodeling in both adult and pediatric populations.

JUAN FERNANDEZ-MIRANDA, MD, was appointed professor of neurosurgery and of medicine, effective July 1. He is the surgical director of the brain tumor, skull base and pituitary centers at Stanford. He specializes in minimally invasive brain surgery, endoscopic skull base surgery, pituitary surgery, open skull base surgery and complex brain tumor surgery.

KIMBERLY KOPECKY, MD, resident in general surgery, was awarded a 2018 Alpha Omega Alpha Postgraduate Fellowship to develop an interactive communication curriculum for surgical residents. She will receive $2,000 over the next year to support her project.

MICHELLE MONJE, MD, PhD, was promoted to associate professor of neurology, effective Aug. 1. Her research explores the molecular and cellular mechanisms of postnatal neurodevelopment, with a particular focus on the origins of pediatric brain tumors and the consequences of cancer treatment.

LORI MUFFLY, MD, was appointed assistant professor of medicine, effective July 1. She specializes in blood and marrow transplantation and cellular therapies for patients with hematologic malignancies, and she develops clinical trials and epidemiologic studies to improve outcomes in adults with acute leukemia.

MICHELLE ODDEN, PhD, was appointed associate professor of health research and policy, effective Aug. 1. Her research examines preventive strategies for chronic cardiovascular and kidney disease in older adults, with a focus on racial and ethnic minorities and the very old and frail. She also studies the preservation of physical and cognitive function in older adults.

MATTHEW WHEELER, MD, was appointed assistant professor of medicine, effective July 1. He is the executive director of the Stanford Center for Undiagnosed Diseases. His research interests include the genetics, mechanisms, screening and treatment of cardiomyopathy, as well as rare and undiagnosed diseases. ISM

Researchers get NIH funding to study tobacco policies, retail environment

Researchers at the School of Medicine and their collaborators at two other institutions will investigate the tobacco retail environment to better understand how it contributes to tobacco-related health conditions and to evaluate the efficacy of tobacco policies in the United States.

Stanford University, the University of North Carolina-Chapel Hill and Washington University in St. Louis jointly received a five-year, $11.6 million grant from the National Institutes of Health as part of an effort to reduce tobacco use, improve public health and provide evidence-based guidance for tobacco-related retail policies.

The new grant establishes a center, the Advancing Science & Practice in the Retail Environment Center, to enable a multidisciplinary team of investigators to identify important relationships between tobacco policy interventions, tobacco use and diseases at the population level.

Nearly $4 million of the grant will go to Stanford to fund two components of the center: a data/statistics core led by Manisha Desai, PhD, professor of medicine and of biomedical data science; and one of three integrated research projects, the Big City Tobacco Control Study, which will be led by Lisa Henriksen, PhD, senior research scientist, and Judith Prochaska, PhD, associate professor of medicine. Both are members of the Stanford Prevention Research Center.

The Stanford team will survey 2,400 adult smokers five times over 2 ½ years and assess how the proximity of tobacco retailers affects smokers who are trying to quit. In addition, the Stanford team will monitor tobacco policy and tobacco use at a population level by analyzing retail sales data from 30 cities.

Researchers at UNC and Washington University will examine tobacco-retailer density and the rate of tobacco-related disease as well as how tobacco is marketed to different socioeconomic groups, and use computational modeling to study how best to address these public health problems with policy changes. ISM

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