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’m very proud of me and the value I placed in my education to reach this point.”

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 as 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 alumus speaker was David Bilder, who earned a PhD in developmental biology in 1993. 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 re-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 and varicose veins,” said toy, PhD, now a scientist at the Asian Liver Center at the Stanford School of Medicine. “These genes are associated with the development of varicose veins, and understanding how they work could help us develop new treatments.”

Using data from the National Institutes of Health’s All of Us Research Program, Toy and his team analyzed the genomes of 436,777 participants who had been diagnosed with varicose veins and compared them to those of 436,777 participants without the condition.

They found that people who are taller are more likely to have varicose veins, even when controlling for factors such as age, sex, weight and ethnicity. The study was published in the journal Circulation.

“The results support the idea that genetics play a role in the development of varicose veins,” Toy said. “This could help us identify new targets for treatment and prevention.”

Varicose veins affect 30 million people across the United States. The condition is more common in women than men, with the peak incidence between ages 45 and 55. While varicose veins are not typically a cause for concern, they can cause discomfort and even pain for some people.

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 they have 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 recommendations for allocating the public health burden of hepatitis B by the year 2030.

“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 Bonnie Lo, PhD, associate professor of health
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 VA Veterans 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 had improved cholesterol profiles in their blood and a decreased risk of either heart disease, abdominal aortic aneurysm, or diabetes, respectively. The mutation in PDE3B, however, is the most intriguing, as 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 narrower sliver of rare genetic anomalies for further analysis through a technique called phenome-wide 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 results of the PheWAS technique gleaned disease risk information from immense databases of genetic information linked to electronic health records.`

**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.

“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 know works for my patients with a particular 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 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 genomics help suggest that this drug can decrease the risk of heart disease by lowering triglycerides, but it’s not proved,” he said. “I would not prescribe it until a randomized trial is completed with cilostazol or a related compound 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 improve the health outcomes 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 drugs that target the same pathway of the PCSK9 mutation are already on the market to reduce the risk of heart attacks. The question is whether that same drug could wear multiple therapeutic hats.

“Misled before’

Drugs that mimic the effects of the ANGPTL4 mutation are still under development, and large-scale testing in humans has yet to begin.

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 Tao, 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.

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**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://stanfordmed.lgbtqplus.org.

**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 Medicine community members and the public.

For more information or to register, visit http://med.stanford.edu/chri/events/symposium.html.

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Please contact him to receive an e-mail version of Inside Stanford Medicine.
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 speaks on behalf of the other hospitals on complex diseases and disorders including cancer treatment, organ transplantation, neuroscience, cardiovascular, 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 care we provide, and for our research, education.

We work with patients to ensure they get the care they need, when they need it.

How would Measure F impact Stanford Health Care?

Entwistle: If passed, Measure F would require Stanford Health Care to limit charges to commercially insured patients to 15 percent above the cost of “direct” patient care. A critical subset of additional expenses covered by providers are included in “direct” patient care — for both inpatient and outpatient care. For academic medical centers, these include necessary overhead, could not be factored in to the cost of care for commercially insured patients. Stanford Health Care also factored in the account for the losses that providers incur when they treat patients insured through Medicare and MediCal and those who are uninsured. Today, providers recover these losses in part through the care they offer to commercially insured patients.

This 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 fragment 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 to no more than 15 percent above the “reasonable cost” of providing “direct” patient care. 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 lay off employees. That’s a lose-lose proposition for everyone.

In the Stanford community, we 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 ultimately, the patients and people we care about and serve.

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 perspectives that are represented in our communities. 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, for both inpatient and outpatient care. Academic medical centers are among those health care providers that said Measure F would fail to improve health care in the city. Access to this health care for the people of our community is critical to the university’s success. We believe Measure F is a threat to 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.

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.

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Q:

A: 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, 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.

The university 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.

From left: David Entwistle, Mary Hawn and Randy Livingston.
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 $35 million over the next five years to pursue 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 School of Medicine researchers,” said Joan Shalowitz, dean of the School of Medicine. “By stretching the limits of our biomedical understanding, our researchers are helping to realize promising new ways to improve human health care more precise, predictive and protractive.”

Two of the Stanford scientists received Pioneer Awards, such as the other five recipients of this year’s Pioneer award, were recognized for their efforts to translate understanding of the basic biology of disease to the development of therapeutics. The other three recipients were recognized for their efforts to develop new ways to use innovative technologies to improve healthcare.

The grant program is part of the NIH Common Fund.

**PIONEER AWARD**

The Pioneer Award provides up to $5.5 million, dispersed 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 tumor cells grow and interact to predict and to predict their progression.

Her research focuses on understanding cancer systems biology, or how genes and proteins 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.

“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 trajectory 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 their genetic makeup and comparing these with virtual tumors simulated under different scenarios. She is also working to measure tumor adaptation during development and tumor progression over time by leveraging new methods to trace cell lineages.

Curtis is co-director of the Stanford Molecular Tumor Triage and Management Program, part of Stanford Cancer Institute, the Canary Center at Stanford for Cancer Early Detection and Stanford BiosX.

Michelle Monje, MD, PhD, associate professor of neuroscience and neurologic 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.

Monje’s award will enable her and her collaborators to develop new tactics for studying how glioma cells form functional circuits with the nervous system and how these circuits change as the cells grow. 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 brain circuit dynamics of high-grade gliomas as the disease evolves.

“With this award, I’ll be building my lab’s expertise in optogenetics and optogenetics capabilities to get a deeper, more detailed view of how gliomas integrate into neural circuitry,” she said. “We hope to identify specific patterns of glioma circuit dynamics that can be genetically 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 $5.5 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 organisms fold to connect or seal off different parts of this genetic blueprint to control cell behavior,” Boettiger said. “My lab is developing new microsurgical 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 genomic technologies to determine which sequences switch directly following decisions.”

The ability to read and understand the distinct three-dimensional blueprint that an organism will eventually seek 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 do not.

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

“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 and how they are related to averaging data across space, time or individuals,” Saggar said.

This new computational framework could both be used for development of personalized strategies of mental illness 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 behavioral sciences and the D.H. Chen Professor, and Anne Brunet, PhD, professor of bioengineering, have won the 2017 Transformative Research Award for a project that seeks to understand how different organ systems communicate with one another or 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 molecule might influence another. To tag and track molecules in different cells and group will use an enzyme called TurboID, which Ting created in her lab five years ago. TurboID carries a molecular marker staked to track the molecules in its immediate proximity.

“Ting said. The idea is to tag a wide range of molecules found in a single type of tissue, such as fat, and subsequently look for those that are present in different tissues, such as muscle,” Ting said. Those with the tag will have come from the fat and can be further investigated to understand what is happening in the fat. The grant totals more than $8 million, of which about $670,000 will be funneled directly to Stanford to support Ting’s continuing efforts to develop 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 the Stanford Neurosciences Institute.

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

OCTOBER 8, 2018   INSIDE STANFORD MEDICINE
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.”

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, Steven 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 — Evan Ashley and James Priest, Stanford; Rima Arnaout and Arul 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; T omasz Nowakowski, Jimmie Ye and Alex Pollen, UCSF; David Schaffer, UC-Berkeley; Melanie Ott, UCSF; Gladstone Institutes
- Imaging complex biological machines in action — Wuh Chiu and John Boothroyd, Stanford; Carolyn Larabell, UCSF; James Sehian, UC-Berkeley

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.
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 whip-like 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 counter-clockwise 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 engineers design tiny swimming robots of the future to be more efficient and effective at maneuvering through the thin film of water over a surface, 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, whip-like 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 developed to study how it moves in relation to light. In his model, when he simulated increased light levels, 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 moves in relation to light, the behavior makes sense for a Euglena swimming in a relatively straight line.

To 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 apply it to other living systems,” Riedel-Kruse said.

As for why nobody had seen this before, Riedel-Kruse said people rarely spent 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 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 are water-dwelling single-celled organisms related to plants, animals and fungi. Riedel-Kruse’s lab studies Euglena in part to better understand how microorganisms navigate their watery worlds.
Toy initially studied epidemiology, the branch of science concerned with 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 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 informed public health policy changes in the Netherlands and in Turkey. After completing her PhD, Toy accepted a fellowship at Harvard to study internationals, 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 medical journals. China also enacted health policy 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 determine what conditions are necessary for the treatment to 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 populations, health ministries can use this information 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 variables amounts to lower the cost of health care. “It also serves as an outreach tool,” she said. By emphasizing that hepatitis B is an infectious disease, Toy said. “Sometimes physicists 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 relationships with other stakeholders.

Toy came to Stanford in 2015 as a postdoctoral scholar to work with Samuel So, MD, executive director of the Asian Liver Center. "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 variables 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.”

**Varicose veins**

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 under the skin. Varicose veins can affect anyone of any age or gender. They are more common in women. Varicose veins can cause discomfort and pain and can be caused by factors such as pregnancy, childbirth, obesity, and aging.

"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 novel translational targets," she said.

Researchers used data from the UK Biobank — both a long-term study and a genetic repository that includes genomic data on 637,536 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 higher risk for the disease," 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 leg, 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**

Typically in a large, genetic study like this one, researchers use genomewide association studies to examine DNA variation that may be associated with a particular disease or illness. Using this method, the researchers identified the 30 regions on chromosome 11 that are 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 with 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."

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, and that we might be looking at a genetic risk associated with varicose veins," Ingelsson said.

He added, "By conducting the largest genome-wide association studies on deep vein disease, we now have a much better understanding of the biology that is altered in people at risk for the disease.”

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

Daniela Zanetti, PhD, a postdoctoral scholar at Stanford, also contributed to the study, which was presented at Uppsala University in Sweden.

The study was supported by funding from the Swedish Research Council, the Knut and Alice Wallenberg Foundation, Stanford's Department of Medicine also supported the work.
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 develop technology and provide evidence-based guidance for tobacco-related retail policies.

The 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 across the nation over the next year to support her project.

MICHELE MONJE, MD, PhD, was appointed associate professor of medicine, effective Aug. 1. Her research focuses on the role of cancer biology in 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.