INSIDE STANFORD MEDICINE

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The Big Data in Biomedicine Conference focused on precision health in action.

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Fitness trackers err in measuring calories

By Jennie Dusheck

Millions of people wear some kind of wristband activity tracker and use the device to monitor their own exercise and health, often sharing the data with their physician. But is the data accurate?

Such people can take heart in knowing that if the device is measuring heart rate, it's probably doing a good job, a team of researchers at the School of Medicine reports. But if it's measuring energy expenditure, it's probably off by a significant amount.

PAUL SAKUMA

Euan Ashley and his team conducted a study to determine how accurately fitness trackers measure heart rate and energy expenditure.

An evaluation of seven devices in a diverse group of 60 volunteers showed that six of the devices measured heart rate with an error rate of less than 5 percent. The team evaluated the Apple Watch, Basis Peak, Fitbit Surge, Microsoft Band, Mio Alpha 2, PulseOn and the Samsung Gear S2. Some devices were more accurate than others, and factors such as skin color and body mass index affected the measurements.

In contrast, none of the seven devices measured energy expenditure accurately, the study found. Even the most accurate device was off by an average of 27 percent. And the least accurate was off by 93 percent.

"People are basing life decisions on the data provided by these devices," said Euan Ashley, DPhil, FRCP, professor of cardiovascular medicine, of genetics and of biomedical data science at Stanford. But consumer devices aren't held to the same standards as medical-grade devices, and it's hard for doctors to know what to make of heart-rate data and other data from a patient's wearable device, he said.

A paper reporting the researchers' findings was published online May 24 in the *Journal of Personalized Medicine*. Ashley is the senior author. Lead authorship is shared by graduate student Anna Shcherbina, visiting assistant professor Mikael Mattsson, PhD, and senior research scientist Daryl Waggott.

Hard for consumers to know device accuracy

Manufacturers may test the accuracy of activity devices extensively, said Ashley, but it's hard for consumers to know how accurate such information is or the process that the manufacturers used in testing the devices. So Ashley and his colleagues set out to independently evaluate activity trackers that met criteria such as measuring both heart rate and energy expenditure and being commercially available.

"For a lay user, in a non-medical setting, we want to keep that error under 10 percent," Shcherbina said.

Sixty volunteers, including 31 women and 29 men, wore the seven devices while walking or running on treadmills or using stationary bicycles. Each volunteer's heart was measured with a medical-grade electrocardiograph. Metabolic rate was estimated with an instrument for measuring the oxygen and carbon dioxide in breath — a good proxy for metabolism and energy expenditure. Results from the wearable devices were then compared to the measurements from the two "gold standard" instruments.

"The heart rate measurements performed far better than we expected," said Ashley, "but the energy expenditure measures were way off the mark. The magnitude of just how bad they were surprised me."

The take-home message, he See FITNESS, page 6

Mouse lemur could serve as ideal model for human disease

By Ruthann Richter

The mouse lemur — the world's smallest primate — has the potential to transform the field of genetics and serve as an ideal model for a wide range of primate biology, behavior and medicine, including cardiovascular disease and Alzheimer's disease, School of Medicine researchers say.

For decades, scientists have relied on mice, fruit flies and worms as genetic models, but despite all their success, these organisms routinely fail to mimic many aspects of primate biology, including many human diseases, said Mark Krasnow, MD, PhD, professor of biochemistry.

Frustrated by the lack of a good study model, Krasnow and his colleagues turned to the mouse lemur and began conducting detailed physiologic and genetic studies on hundreds of these petite, docile creatures in the rainforests of Madagascar.

Working in a Stanford-funded lab on the island country, the scientists report that they already have identified more than 20 individual lemurs with unique genetic traits, including obesity, high

ROBERT SIEGEL

Mouse lemurs are primates about twice the size of a mouse and live exclusively in Madagascar.

cholesterol, high blood sugar, cardiac arrhythmias, progressive eye disease and motor and personality disorders. Their hope is that continued study of these abundant primates could lead to a better understanding, and possibly better treatments, of these and other conditions in lemurs and humans.

"I think mouse See LEMUR, page 7

Cost-effective ways to combat HIV risk among injection-drug users identified

By Nicole Feldman

With the abuse of opioids on the rise in the United States, Stanford researchers are concerned that increased HIV transmission from shared needles won't be far behind.

"There's an opioid epidemic in our country, and there's a real public health crisis associated with injecting," said Cora Bernard, a graduate student in management science and engineering. "We think it's important to understand what investments give highest value because HIV prevention programs, and especially programs that reduce the prevalence of injection drug use, can have outsized, positive impact on individuals, families and public safety."

Bernard is the lead author of a study on prevention programs that could head off a resurgence of HIV and perhaps decrease the effects of the opioid crisis. The study was published online May 24 in *PLOS Medicine*. The senior author is Margaret Brandeau, PhD, professor of management science and engineering.

In July 2016, Bernard and her co-authors published a different study examining pre-exposure prophylaxis, or PrEP, a pill that reduces a person's risk of infection when they come into contact with the HIV virus. The researchers found that PrEP was effective, but expensive.

The new study examines alternatives that also reduce the risk of HIV infection but are more cost-effective. They created a model to determine how many quality-adjusted life years — a metric that incorporates both life expectancy and quality of life — a person could gain from four HIV prevention methods, and what those years would cost.

"The dynamics of HIV prevention and treatment are complex," Brandeau said. "Our model allows us to evaluate the costs and See HIV, page 6

TRAVEL_MASTER / SHUTTERSTOCK.COM

A new study assesses prevention programs that could head off a resurgence of HIV and perhaps decrease the effects of the opioid crisis.

Inspiring Change Leadership, Spirit award winners announced

By Mandy Erickson

Four staff members have been selected as this year's winners of the School of Medicine's Anne G. Crowe Spirit Award or the Inspiring Change Leadership Award.

Spirit Award winners are selected for their outstanding dedication, initiative, motivation, positive attitude and customer service. This year's recipients are Christine Hendricks, clinical program manager in the Department of Emergency Medicine, and Ana Mezynski, administrative associate for the Stanford-Surgery Policy Improvement Research & Education Center.

The Inspiring Change Leadership Award, which goes to staff members who have implemented processes that improve the school, was given to Kim Walker, learning program manager in the Office of Information Resources & Technology, and Mary Ayers, director of learning spaces for Educational Programs and Services and the Center for Immersive and Simulation-based Learning.

Each winner will receive $3,000.

Christine Hendricks

Ana Mezynski

Kim Walker

Mary Ayers

Christine Hendricks

As the administrative staff for the Department of Emergency Medicine gathered for an award announcement, Hendricks had her camera out, all set to take a photo of the winner. "There I was, ready to take pictures of someone else, and it was me," she said, laughing.

It was typical of Hendricks, whose co-workers say is always ready to assist, always humble, always gracious. "You never feel like you're interrupting her, though of course you are," said Stephanie Edelman, director of finance and administration for surgery and for emergency medicine. "She makes everyone feel that way."

Hendricks, who has been with Stanford Medicine for 17 years, took on her current role five years ago. As manager of the administrative staff, she's the glue that binds the team, the jill-of-all-trades who solves problems large and small. Among other tasks, she puts together the department newsletter and organizes meetings, celebrations, faculty retreats and graduation ceremonies. "My job is basically making sure everyone is taken care of," she said.

Her job exposes her to the work of the faculty, including international programs and other projects outside the walls of the Emergency Medicine Department. "Everyone does so many different things," she said. "I'm always learning something new."

The award brought her to tears, she said. "I've always felt appreciated in the department, but they remembered these small details that made a big impact. It was just a great feeling."

Ana Mezynski

Knowing what her family means to her, Mezynski's co-workers brought in her youngest child, her 14-year-old daughter, when Mezynski's award was announced.

"I was really moved when I saw her," Mezynski said, adding that her award is "a legacy for my two children."

Mezynski plans events for the Stanford-Surgery Policy Improvement Research & Education Center, updates its website — which she developed — and oversees the office's day-to-day needs, such as ordering supplies and maintaining the directory. She also assists the postdoctoral scholars and visiting scholars in the Division of General Surgery in applying for grants and obtaining visas.

As the support-staff member for a group of researchers, recently she has started collecting data herself: She produces a quarterly report of S-SPIRE's accomplishments, such as papers published, grants awarded and consultations held with researchers who need help on their projects.

"I face a lot of challenges, and I like that about my job," Mezynski said. "If I don't have the answer, then I do some research and I find the answer.

"The S-SPIRE Center is giving me a lot of opportunities to grow."

It was just this sort of enthusiasm for learning that earned her the award. "She takes initiative," Edelman said. "She just pushes forward with whatever needs to be done, and comes up with ideas to make the process better. She has a huge work ethic."

Kim Walker

For the online medical education courses they produce, Walker's instructional design and production team at IRT goes way beyond training a camera on a professor in front of a whiteboard.

Her team of animators, graphic designers and videographers film skits of actors playing physicians, create animated patient scenarios, and incorporate interactive activities such as role-playing. "We are being innovative and learning from every project," Walker said.

The result, according to Mark Trenchard, director of academic and interactive technology, is "higher quality experiences and more effective content for our learners."

"From day one, Kim looked above and beyond the way we were building the courses," Trenchard said. "She inspires and is able to build high-performing and high-morale teams."

When Walker started 2 ½ years ago, the courses were all continuing medical education for physicians. But her team is now producing courses for undergraduates, residents and health care workers around the globe.

The courses cover all aspects of medicine, including transgender health, opioid addiction and prescribing practices. Walker said the transgender health course "has had an incredibly positive impact on the people who have taken the course, an enlightening on what it means to be born into a life that doesn't match your body."

Walker said she's honored to be part of such life-changing medical education. She's also inspired by her production team: "I feel very blessed to work with so many wonderful, talented, hardworking, creative individuals, and to be able to touch people's lives through medical education," she said.

Mary Ayers

Every year, Ayers and her team face an enormous, Tetris-like task: scheduling the 90 classrooms for the School of Medicine. Policies and priority levels complicate the process, as does the fact that the number of spaces have doubled since the Center for Immersive and Simulation-based Learning opened in 2011.

This year, Ayers decided to streamline the system before the scheduling began in June using a lean launch initiative. Working with her "users" — those who ask for classroom space — Ayers' team addressed the glitches in the system. They redesigned the request form and rewrote the instructions, among other improvements.

Along the way, Ayers tested any changes with the users and tweaked the system to make it even better. Once it was ready to go, she provided training for the new, improved system.

"Now, anyone requesting activities in the center better understands what we need, and we don't have to go back to ask for more information," Ayers said. "It's much more user-friendly."

Susan Eller, assistant dean for immersive and simulation-based learning, said that because of Ayers' improvements, users will know the schedule two weeks earlier, allowing them more time to coordinate faculty and student schedules.

She added that Ayers' 24 years of building relationships at Stanford were instrumental in the success of the relaunch: "People don't like change, but so many people know and trust Mary they were willing to go with it."

Ayers said that the scheduling relaunch has taught her and her colleagues about improving processes, and they're planning to apply that knowledge to other functions, such as purchasing.

"With a redesign process like the one we used, people feel like they have a voice," she said. "It brings people in, which ultimately makes it work." ISM

Mary M. and Sash A. Spencer Center for vision research established

By Eileen DiFranco

Stanford University has announced the establishment of the new Mary M. and Sash A. Spencer Center for Vision Research, thanks to a generous gift pledged by Mary Spencer in honor of her late husband, Sash.

The new center, at the renowned Byers Eye Institute, will support innovative vision research and interdisciplinary collaborations across the Stanford campus.

Connecting research to care

The new Mary M. and Sash A. Spencer Center for Vision Research at Stanford is at the heart of an ambitious vision for advancing research and creating new diagnostics and therapeutics that will change patient care. The goal of the center is to develop new cures and treatments for the most challenging eye diseases, such as macular degeneration and glaucoma, which impact the lives of millions of people — often leaving them partially or wholly without sight.

COURTESY OF MARY SPENCER

Sash and Mary Spencer pledged a gift to support the creation of a vision-research center.

The center will be at the forefront of the search for new diagnostics and therapies, both to prevent vision loss and to restore sight, while offering patients access to the latest research, technologies, clinical trials and treatments. It will build on the Byers Eye Institute's reputation for innovation and patient-centered care.

Lloyd Minor, MD, dean of the School of Medicine, said, "We are optimistic that with the establishment of this new center, significant advances in vision science will be translated into improved patient care, transforming the lives of millions suffering from eye disease the world over." Of Mary Spencer's gift, he added,

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STANFORD MEDICINE

Researchers' technique pinpoints 'partners in crime' of cancer genes

By Krista Conger

Batman and Robin. Sherlock Holmes and Dr. Watson. Fiction is full of dynamic duos that work together to accomplish amazing feats. When one partner is out of commission, the other steps in to make sure the job gets done. But if both are missing in action, the outcome is likely to be dire.

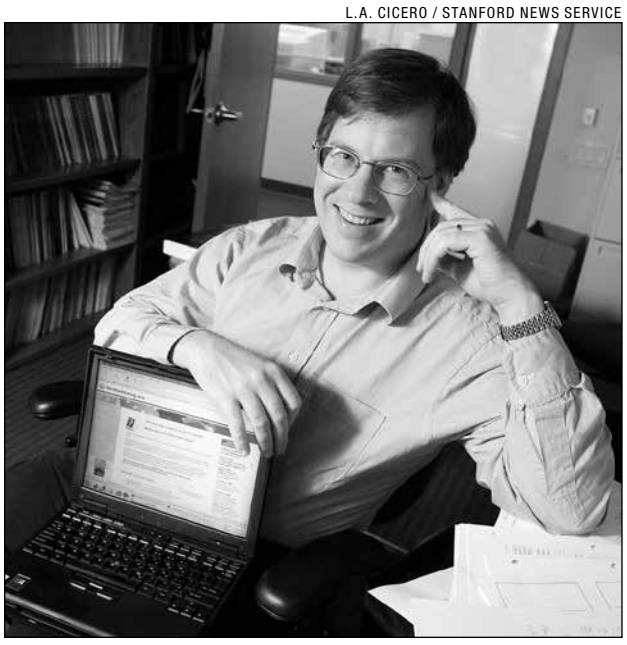
Cancers also often rely on pairs of complementary genes to keep their cells plugging along as they spin increasingly out of the bounds of normal cellular control. If one partner is mutated, the other springs to the rescue; if both are compromised, the cell dies. Genes that work in this way are called synthetic lethals, and cancer researchers' ears perk up when one member of the pair is a known cancer-associated mutation. Blocking its partner could be an attractive therapeutic target that would specifically kill cancer cells while sparing normal cells without the mutation. But until now it's been difficult to identify these partners in crime.

Now researchers at Stanford have devised a new computer algorithm to churn through piles of existing data to suss out and target these genetic understudies in primary human tumors. Doing so is likely to lead to new, less-toxic treatments for many cancers, they believe. They are now collaborating with oncologists at Stanford and at M.D. Anderson Cancer Center in Texas to use the algorithm, which they've called MiSL, to find new, mutation-specific therapies for patients with a variety of cancers.

"We're entering a new era of precision health," said associate professor of medicine Ravi Majeti, MD, PhD. "Using data from real human tumors gives us important, fundamental advantages over using cancer cell lines that often don't display the same mutation profiles. We've found that, although many known cancer-associated mutations are difficult to target clinically, their synthetic lethal partners may be much more druggable."

The researchers tackled 12 different types of cancers and over 3,000 cancer-associated mutations to identify thousands of new genetic partnerships that could be amenable to drug treatment. In particular, they found that 17 of the 89 potential synthetic lethal partners for a well-known, leukemia-associated mutation are likely to be susceptible to drugs that are either already clinically available or are under development.

L.A. CICERO / STANFORD NEWS SERVICE



David Dill says the algorithm has found more connections than expected between genes that work together in cancer cells.

Majeti and professor of computer science David Dill, PhD, share senior authorship of the study, which was published online May 31 in *Nature Communications*. Research associate Subarna Sinha, PhD, and postdoctoral scholar Daniel Thomas, PhD, share lead authorship.

The collaboration between the Majeti and Dill labs developed through Stanford's Center for Cancer Systems Biology, which aims to identify broad biological patterns in the methods cancer cells use to evade the immune system.

Sifting through the mess

The researchers capitalized on the fact that cancer cells are often a genomic hot mess. As they proliferate out of control, they play fast and loose with the normal rules for DNA duplication and cellular division. It's not uncommon for genes to be summarily deleted from the genome or, conversely, to be "amplified" so that they occur two, three or more times in the cells' DNA.

In this study, the researchers taught the computer a simple "if this, then that" concept to help them identify pairs of genes whose expression levels were co-dependent — a hallmark of synthetic lethals.

"We were looking for situations in which, if gene A is mutated, gene Y is amplified to compensate for the loss of function of gene A," said Dill, who is the Donald E. Knuth Professor in the School of Engineering. "Conversely, gene Y is only ever deleted in cells in which gene A is not mutated." In other words, these genetic partners have each others' backs.

> "We're entering a new era of precision health."

The researchers applied their technique to data stored in a national human cancer database called The Cancer Genome Atlas. The software sifted through DNA sequences and gene expression levels to identify situations in which genes were either more highly expressed in the presence of particular cancer-associated mutations than when the mutation was absent, or genes that were rarely or never deleted in the presence of the mutation. Because the analysis was computerized, it could be conducted without any preconceived notions about what genes might be working together in the cancer cells.

"We found these strong relationships much more often than we had expected, even among seemingly unrelated genes," said Dill.

The researchers analyzed more than 3,000 known cancer-associated genes and identified more than 140,000 potential synthetic lethal partners through a study of the DNA sequences of the cells. They winnowed this number down by limiting the prospects to only those that displayed a true difference in gene expression levels of the partner based on whether the first gene was mutated. In most cases, this narrowed the contenders down to 50 or fewer for each mutation.

Powerful tool

They found that MiSL pinpointed some synthetic lethals that had previously been identified by other means — confirming that their approach was working. But they also identified some new relationships, including one between a mutation in a gene called IDH1 that's associated with the development of leukemia and another gene called ACACA. They validated this synthetic lethal partnership by a variety of tests in laboratory grown cells and human tumor tissue.

STEVE FISCH

Ravi Majeti and his collaborators have developed an algorithm to find new pathways that may help them better target cancer cells.

"We have just scratched the surface of what we think we can learn with MiSL," said Majeti. "It's an incredibly powerful way to analyze large amounts of data to quickly identify relationships of potential interest, and it's likely to make drug development much more efficient and quick."

Interestingly, the researchers found that some synthetic lethal pairs predicted by MiSL were found in multiple human cancers. In particular, the genes tended to be involved in pathways of broad biological significance, including the Krebs cycle, which releases energy stored in carbohydrates, fats and proteins; the DNA repair machinery used by cells to correct genetic mistakes; and the Wnt signaling pathway, which has been shown to be critical in normal development and many human cancers.

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors are hematologist Steven Chan, MD; research assistant Damoun Torabi; postdoctoral scholar Andreas Reinisch, MD, PhD; former CIRM Bridges intern David Cruz; resident Andy Chan, MD; and assistant professor of radiation oncology Erinn Rankin, PhD.

Majeti is a member of Stanford's Bio-X, the Stanford Cancer Institute, the Stanford Institute for Stem Cell Biology and Regenerative Medicine and the Stanford Child Health Research Institute. Dill is a member of Bio-X.

The research was supported by the National Institutes of Health, the New York Stem Cell Foundation, the Leukemia and Lymphoma Society and a CJ Martin Overseas Fellowship.

Majeti, Dill, Sinha and Thomas have filed an international patent based on the findings in this paper.

Stanford's departments of Medicine and of Computer Science also supported the work. ISM

Vision

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"This will create a remarkable legacy for Sash and Mary Spencer for generations to come. We are incredibly grateful for her trust and generosity."

According to Jeffrey Goldberg, MD, PhD, Stanford's chair of ophthalmology and director of the new center, "Many diseases of the eye still lack clear and effective methods of prevention, treatment or cure. Although much research is underway, bridging the chasm from the lab to clinical testing and ultimately to proven therapies remains the core challenge to making real progress."

He added, "Our goal for this new center is to bring together teams of interdisciplinary experts in genetics, imaging, stem cell and neurobiology with leaders in vision science. By harnessing the combined talents and energy available at Stanford and beyond, we can uncover novel therapies and bring them more rapidly to human trials — to real patients — so that others can benefit in the nearer term."

The center will also work toward the development of new diagnostics and methods to help predict eye diseases before they occur, leading to preventive and more personalized care — the foundation of Stanford Medicine's focus on precision health.

A legacy of excellence

Mary Spencer, who suffers from the early effects of macular degeneration herself, believes this new center at Stanford will bring the brightest scientists together at the right place to make a lasting impact on the field of vision science.

With the help of her philanthropic commitment, she hopes to witness in her lifetime the discovery of treatments for some of the worst eye diseases and also to create a legacy of excellence that honors her late husband's memory. Goldberg and the early promise shown by his work using magnetic nanoparticles to promote regenerative therapies for the eye was a major factor in Spencer's decision to support the establishment of the new research center.

"I hope that Jeff's vision for this center will be realized and it will become a place where leading vision scientists from across the country and the world will come together and share their knowledge," Spencer said. ISM

Experts: Integrating diverse kinds of data key to precision health

By Jennie Dusheck

Environmental, behavioral and social data could help researchers and clinicians prevent disease in whole populations — not just diagnose and treat disease — according to speakers at Stanford's fifth annual Big Data in Biomedicine Conference.

The conference, held May 24-25 at the Li Ka Shing Center for Learning and Knowledge, drew about 500 attendees and 2,000 remote viewers. Titled "Big Data in Biomedicine: Transforming Lives Through Precision Health," the conference focused on precision health in action.

A series of talks and panels highlighted, for example, the National Institutes of Health-funded Precision Medicine Initiative, which will use data from a million volunteers to build a future where prevention and treatment are tailored to individuals based on their genes, microbiome, health histories lifestyles and diet, and the Chan-Zuckerberg Initiative, which aims to rid the world of disease by 2100. Speakers also discussed applications of big data to cardiovascular disease and cancer; the use of artificial intelligence in imaging; and digital health and technology.

PHOTOS BY ROD SEARCEY

The Big Data in Biomedicine Conference, which was held May 24-25, drew about 500 attendees and 2,000 remote viewers.

(Clockwise from left) Lloyd Minor speaks May 24 at the conference, which was held at the Li Ka Shing Center for Learning and Knowledge. Eric Topol gives a talk at the conference, where he said he wants physicians to make greater use of tools and technology focused on disease prevention. Jessica Mega said Verily's Project Baseline will serve as a test bed to think about the next generation of tools needed to understand human physiology and variability.

The key to transforming lives through precision health, experts at the conference said, is the integration of diverse kinds of data sets, including sequencing and imaging data, gene expression data and also behavioral data, such as that from fitness trackers. Finding ways to combine and explore such cross-disciplinary data sets will be key to the focus on prevention, they said.

"For years, health care really has been about sick care; it's been about treating severe acute diseases or their chronic manifestations," Lloyd Minor, MD, dean of the School of Medicine, said during remarks on the first day of the conference. "And there's been comparatively little attention either in research or care delivery on prediction and prevention. But that's all changing today, because of the work being done in this room, because of the work being done at Stanford."

Advocating greater focus on prevention

Eric Topol, MD, a professor of genomics at the Scripps Research Institute, gave a passionate talk in which he criticized U.S. medical care and advocated for a greater focus on prevention.

The key, Topol said, is moving "from where we see people as all the same, at the 50,000-foot level — which is the way medicine is practiced and the way we give out drugs and diagnoses and do screenings — to ending this concept of an 'average person,' who doesn't exist."

"Where we are in 2017 is remarkably primitive," Topol said, quickly reviewing a series of facts about U.S. health care. Mass screenings, for example, often do more harm than good. Of every 10,000 mammograms, Topol said, only five actually benefit the patient, while thousands are false positives that can result in actual harm. He also cited the high rate of medical errors and misdiagnoses, despite an annual health care budget of $3.4 trillion in 2016

"We have to be able to do better than that, you would think, if we can define each individual, which we haven't had the tools to do — until now," he said.

Mapping humans

One way medicine can improve is by mapping human beings using approaches that resemble the geographic information system maps that geographers, mapping apps and urban and county planners use to understand different layers of information about the world, Topol said.

Today, biomedical researchers have the capacity to quantify and track a person's environment, behavior, dynamic physiology and proteomics through time and across whole populations, Topol said. Sensors can track the data while algorithms can integrate and interpret multiple data streams.

Such data shouldn't be understood like the black box approach of Netflix guessing which movies you'd like, though, said Hemant Taneja, PhD, managing director at the venture capital firm General Catalyst, who spoke during a panel discussion on digital health and technology. We need a higher bar for biological data such that not only can we predict the consequences of certain combinations of factors, but also know the biological mechanisms that cause those effects, he said

"Today you can accurately track your blood pressure through your watch," said Topol, adding that it's possible to see in real time how your blood pressure reacts to heavy traffic or a heated discussion with your spouse. And it's now so easy to monitor blood sugar levels that healthy individuals who don't have diabetes can monitor their blood glucose as a preventive measure.

> **"Our job is to make sure we accelerate the development and implementation of precision health."**

Topol also described a portable ultrasound device that can create an image of the heart beating. He said it makes an old-fashioned stethoscope obsolete. "Why would you listen to 'lub-dub' when you can see everything?" Topol said.

Preventive health at population level

Apply such measurements to 10,000 people, as in the Baseline study by Verily, Duke and Stanford, or a million people, as planned for Precision Medicine Initiative, and you can start to see patterns, experts at the meeting said. Both researchers and clinicians can ask and answer specific questions about which factors are associated with which outcomes.

Such population-level approaches to preventive health care are inspiring more interest in health care inequity and biases in research, some speakers said. Although about two-thirds of people living in the United States are of European ancestry, participants in medical research trials were 96 percent European-American in 2009; by 2016, it was 81 percent European-American, according to Usha Menon, PhD, RN.

Menon, a professor and associate dean for research and global advances at the University of Arizona, suggested a number of strategies for increasing diversity within biomedical research, including, for example, engaging citizen advisory boards in the design of studies and targeting messages. "We have been telling people to stop smoking — for how long?" she asked. "The key is to target and tailor to culture, to what is most relevant to that individual."

Topol and cardiologist Robert Harrington, MD, professor and chair of medicine at Stanford, discussed the possibility that letting data streams and algorithms do much of the work of examining, monitoring and diagnosing patients could give practicing physicians more opportunity to form the intimate bond that doctors once had with patients. Harrington brought up Stanford's Presence, a center whose focus "is try to bring some of the intimacy and humanity back into medicine," he said.

Project Baseline

Verily, one of Alphabet's life sciences units, recently launched Project Baseline with the goal of enrolling 10,000 participants who will share their biomedical data. A long-term goal of the project is to set up scalable and standardized tools for acquiring, organizing and analyzing data, said Jessica Mega, MD, MPH, Verily's chief medical officer, during a talk at the conference. Formerly called Google Life Sciences, Verily has a variety of projects in development, from wearable sensor devices to big data studies.

"We also want to create a test bed for a number of new tools and devices that are out there," Mega said. For example, glucose and atrial fibrillation monitoring devices can provide a stream of data that's valuable to patients and their doctors, valuable to researchers and valuable to whole populations that can eventually benefit from the resulting insights.

"But that's the known signal," Mega said. "As each of us is sitting here, in this room, we are giving off our heart rate and our galvanic skin response. There's digital exhaust all around us that we're not capturing. Some of it may be actionable, some of it may not be. But until we look we won't know."

Project Baseline, Mega said, will serve as a test bed to think about the next generation of tools needed to understand human physiology and variability. The holy grail, she said, is to get in front of disease to know ahead of time that an individual needs help taking preventive measures.

Stanford University President Marc Tessier-Lavigne, PhD, exhorted the audience, "as hard as you are working on these problems, double down again."

"Our charge, our responsibility," he said, "is to make sure we get to precision health tomorrow and not 10 years or 20 years from now. We know it will be a reality eventually. Our job is to make sure we accelerate the development and implementation of precision health."

ISM

Drug for refractory psoriatic arthritis shows promise in large clinical trial

By Bruce Goldman

In a pivotal phase-3 clinical trial led by a School of Medicine investigator, patients with psoriatic arthritis for whom standard-of-care pharmaceutical treatments have provided no lasting relief experienced a significant reduction in symptoms, including joint tenderness and swelling, when they were given a new drug.

The 24-week randomized, double-blind, placebo-controlled trial was conducted at 109 centers in 10 countries and involved more than 300 adults for whom available biologic drugs — the standard of care for this painful autoimmune condition — had lost their efficacy or lacked it in the first place.

Results of the trial were published online May 24 in *The Lancet*.

Left untreated or treated unsuccessfully, psoriatic arthritis can progress to induce severe joint and bone damage and functional disability, said Mark Genovese, MD, a professor of immunology and rheumatology at Stanford and the study's senior author.

In the trial, known as SPIRIT-P2, 314 patients received regular injections of either a biologic drug, ixekizumab, or a placebo for 24 weeks. The trial was sponsored by Eli Lilly & Co., the drug's manufacturer.

Treatment with ixekizumab resulted in more than 50 percent of the participants having at least a 20 percent reduction in the number of tender and swollen joints, significantly outperforming the placebo, said Genovese. Few serious adverse events were reported for patients receiving the drug, or the placebo, he said.

The search for lasting relief

About one in 200 adults in developed countries lives with psoriatic arthritis. Like the more common rheumatoid arthritis, which affects nearly 2 percent of the population, psoriatic arthritis is an inflammatory autoimmune disease whose symptoms — including stiffness, pain and swelling of several joints — typically emerge between the ages of 30 and 50.

The two syndromes differ, though, in their constellation of symptoms. For example, psoriatic arthritis manifests most often in the lower extremities and is associated with the autoimmune skin condition called psoriasis, in which raised red, scaly patches appear on the skin. Although psoriatic rashes most often precede the onset of the arthritic stage, the reverse can also be the case.

Three of the 10 top-selling drugs in the United States in dollar sales — adalimumab, etanercept and infliximab — are biologics prescribed for psoriatic arthritis as well as for the more common rheumatoid arthritis. These three drugs share a common property: They block the action of a pro-inflammatory substance called tumor necrosis factor. Secreted by various immune cells, TNF stimulates the immune response and accompanying inflammation.

NORBERT VON DER GROEBEN

Mark Genovese led a multisite trial that points to a promising therapy for patients whose psoriatic arthritis doesn't respond to other treatments.

However, despite the availability of TNF inhibitors, "only about half of psoriatic arthritis patients who are given TNF inhibitors get better," said Genovese.

Although the ultimate cause of the disease remains unknown, there was a good clinical rationale for hoping it might be responsive to ixekizumab. For the last decade or so, Genovese said, another pro-inflammatory substance called IL-17 has been drawing the attention of immunologists focusing on psoriasis and psoriatic arthritis.

Ixekizumab works by blocking IL-17. The drug, an injectable monoclonal antibody, is already commercially available for the treatment of psoriasis, for which it has been remarkably effective, said Genovese. And in an earlier Lilly-sponsored phase-3 trial, ixekizumab was shown to be effective for psoriatic arthritis patients who had not yet been treated with biologic drugs such as TNF inhibitors. (Another approved monoclonal-antibody that targets IL-17, secukinumab, was approved in 2016 for psoriatic arthritis.)

Less pain and swelling

Over the 24-week duration of the latest trial, 109 participants received ixekizumab every two weeks; 94 received placebo injections every two weeks; and 111 alternated every two weeks between getting injections of ixekizumab and the placebo. While 19.5 percent of patients who received only the placebo injections were judged to have met the trial's specified clinical endpoint — at least a 20 percent reduction in the number of tender and swollen joints — the response rate among those getting the real drug every four weeks was 53.3 percent. Those getting the drug every two weeks didn't do any better and were slightly more prone to side effects, such as a mild reaction at the injection site.

Although any treatment that works by blocking the immune system's ability to mount an inflammatory response should be carefully monitored for its potential to render the body vulnerable to infectious disease, there were few observed differences in this category between recipients of placebo versus active drug given every four weeks, Genovese said.

Lilly has filed for approval of the drug by the U.S. Food and Drug Administration. Genovese has served as a consultant to Lilly.

Other co-authors of the study are affiliated with multiple institutions in diverse locations, including the University of Queensland, in Australia; Guy's & Thomas' NHS Foundation Trust, in London; St. Luke's International University, in Tokyo; Memorial University, in Newfoundland, Canada; Lapeyronie Hospital, in Montpelier, France; Charite University Medicine Berlin, in Germany; and Eli Lilly and Company, in Indianapolis.

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

Karl Deisseroth wins 4 million euros Fresenius Research Prize

By Bruce Goldman

Karl Deisseroth, MD, PhD, a Stanford professor of bioengineering and of psychiatry, has won the 2017 Fresenius Research Prize for his pioneering work in two distinct biomedical technologies — optogenetics and hydrogel-tissue chemistry — and for exploring his clinical specialty, depression, at the level of its underlying neural circuitry.

Deisseroth, who holds the D.H. Chen Professorship and is a Howard Hughes Medical Institute investigator, accepted the award May 31 at a ceremony in Berlin. He also gave a talk, followed by a symposium, on June 1.

The prize is presented every four years to a single scientist by the Else Kroner-Fresenius Foundation in Germany. The prize — the world's most valuable for scientific achievement — comes with a cash award of 4 million euros ($4.47 million): 3.5 million euros for Deisseroth's laboratory, and 500,000 euros for his personal use.

Deisseroth is only the second scientist to receive the prize, which was launched in 2013 and recognizes achievement in medical research. The 2013 recipient was Yale University immunologist Ruslan Medzhitov, PhD.

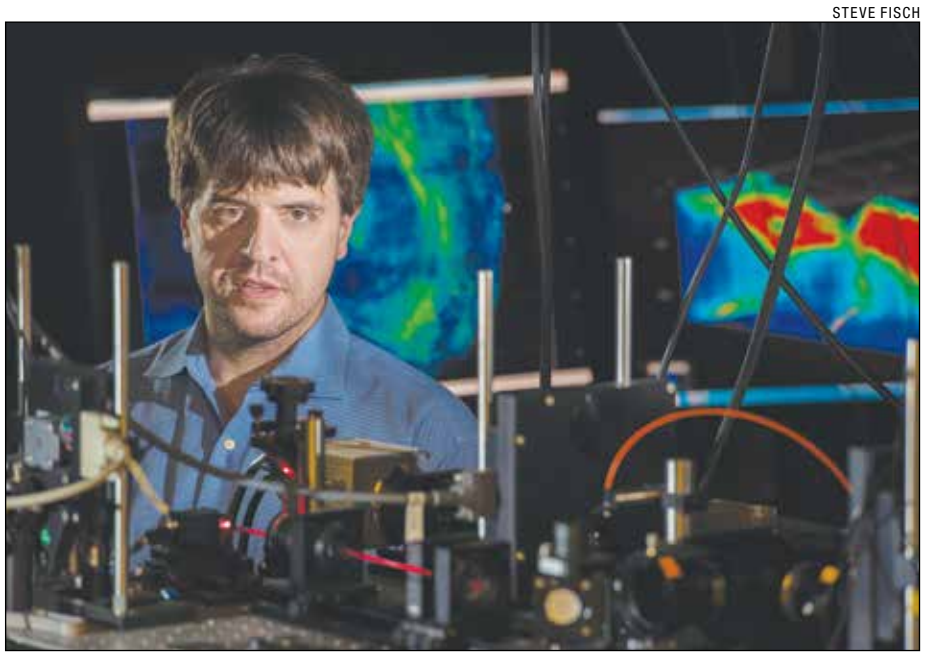
"We are proud that Karl has been recognized for his groundbreaking discoveries," said Stanford University President Marc Tessier-Lavigne, PhD. "Application of his pioneering technologies by scientists worldwide is accelerating understanding and development of therapies for debilitating neurological and psychological diseases, and Karl's own research has provided deep insight into circuit mechanisms of depression. Karl's work exemplifies how brilliant scientific research can improve lives and improve our world."

Many honors to his name

Deisseroth's scientific achievements have won him many other honors, including the Harvey Prize, to be awarded this June; the Massry Prize (2016); the Dickson Prize in Medicine (2015); the Breakthrough Prize (2015); the Keio Medical Science Prize (2014); and the Richard Lounsbery Award (2013).

Lloyd Minor, MD, dean of the Stanford School of Medicine, noted that Deisseroth continues to see psychiatric patients on a regular basis. "Karl speaks of the profound impact it's had on him to know and treat patients with psychiatric disorders and to see firsthand the debilitating nature of these disorders and their effects on patients and their families," Minor said. "His research promises to one day enable millions of people with mental illness to be treated much more effectively than they are today."

STEVE FISCH



Karl Deisseroth was honored for his pioneering work in optogenetics and hydrogel-tissue chemistry, as well as for exploring his clinical specialty, depression, at the level of its underlying neural circuitry.

Pioneered in Deisseroth's lab between 2004 and 2009, optogenetics is a technology that allows scientists to precisely manipulate nerve-cell activity in freely moving animals. Genes encoding light-sensitive proteins, derived from microorganisms, are inserted into targeted nerve cells. As a result, these cells' signaling activity can be turned on or off with the flick of a switch by a pulse of laser light, delivered through a hair-thin optical fiber that has been implanted into the animal's brain. Scientists can deduce the role played by particular nerve cells, relays and circuits by observing the effects of these manipulations on the animal's behavior.

Making tissue transparent

Hydrogel-tissue chemistry, developed in Deisseroth's lab between 2009 and 2016, renders intact tissue samples — and even entire organs of small animals — both transparent to light and permeable to bulky molecular probes. It involves replacing the tissue's fatty substances, which impede transparency, with a hydrogel matrix that not only permits the transmission of light but also permits the transit of large molecules, such as labeled antibodies or oligonucleotides, which can pinpoint the presence of particular proteins or DNA sequences on or in the tissue's constituent cells.

With the help of the sophisticated methodologies developed in his lab, Deisseroth has co-authored many papers on the underpinnings of depression. He and his team have teased apart the separate neural circuits implicated in different aspects of this multifactorial disorder, such as anhedonia (the failure to experience pleasure) versus hopelessness (the inability to rise to a challenge).

Deisseroth's lab is now taking advantage of high-powered data-collection, data-storage and data-analysis methods that have only recently become available. "We're starting to do whole-brain analysis, collecting information from every cell in the brain and getting insights from not leaving anything out," he said.

It's rare for a researcher to achieve even one breakthrough technology. The development of two such game-changers, as in Deisseroth's case, is widely considered remarkable. Still, he said, "Our primary goal isn't to develop new methods for their own sake, but to design techniques that help us answer the questions we want to answer. We're just biologists." ISM

OBITUARY

Stanford infectious-disease expert Kenneth Vosti dies at 88

By Bruce Goldman

Kenneth Vosti, MD, professor emeritus of medicine at the School of Medicine and an expert on urinary tract infections, died April 26 at his home on the Stanford campus after a long illness.

During the decades he served on the Stanford faculty, Vosti published dozens of papers, taught multiple generations of students and held several administrative posts at the medical school, including acting chief of the Division of Infectious Diseases, director of the clinical microbiology lab and associate dean for student affairs.

Vosti was admired for his wisdom and kindness and venerated for his listening ability, empathy and commitment to student issues, said Neil Gesundheit, MD, MPH, associate dean for advising and professor of medicine.

"He was extraordinarily warm and nonjudgmental," said Gesundheit, who first met Vosti nearly 40 years ago, when Gesundheit was doing his internship at the medical school and Vosti was leading the Division of Infectious Diseases. "He looked after his students as he did his own children.

'Committed citizen of the university'

"He was an extraordinarily committed citizen of the university who not only taught in our classrooms and practiced in our hospitals but lived on campus," Gesundheit said.

For Vosti, Stanford turned into a family affair. He earned his bachelor's and medical degrees from the university, and his brother also earned a Stanford medical degree. His four daughters all attended Stanford as undergraduates, and two of his grandchildren have earned degrees from Stanford.

Kenneth Vosti

Vosti turned a visual impairment — he eventually became legally blind — to his advantage. "It's made me a better listener," he said wryly in a 1984 interview.

In 2013, Vosti was honored as the first recipient of the Stanford University Medical Center Alumni Association's Reach, Inspire, Serve and Engage Award, which recognizes individuals who have demonstrated exceptional dedication to Stanford Medicine and the alumni community through acts of leadership, volunteerism, mentoring and teaching.

In addition, the Division of Infectious Diseases presents an annual award in his name: The Kenneth Vosti Teaching Award for Excellence in Teaching.

"Kenneth Vosti's contribution to Stanford — as an educator, as a researcher and as a caring administrator — was immense," said Lloyd Minor, MD, dean of the School of Medicine. "He advanced our understanding of infectious disease and of the medical-training process itself. We will all miss him."

Modesto native

Born Sept. 15, 1928, in Modesto, California, Vosti grew up on ranches in Salida and Modesto. He never outgrew his love of wilderness and outdoor activities. After two years at Modesto Junior College, he matriculated at Stanford in 1948 and, on graduating in 1950 with a bachelor's degree in medical science, moved on to the Stanford School of Medicine. He earned an MD in 1953. He completed an internship, as well as a fellowship in infectious diseases, at the University of Illinois Research and Education Hospital and a residency the West Side Veterans Administration Medical Center in Chicago.

In 1957, Vosti joined the U.S. Army. Assigned to the Walter Reed Medical Research Unit, he drove a new, red-and-white Chevrolet Bel Air from Chicago to Fort Detrick, in Maryland, to report for duty. The next year, he met and became engaged to Anne Merrick, a graduating student at nearby Hood College. They married in 1959.

Recruited by Stanford that year, Vosti joined the medical school's Division of Infectious Diseases as an instructor and founding member. In 1962, he became an assistant professor, and in 1964 he was appointed chief of the division, as well as assistant Stanford Hospital epidemiologist. He was promoted to associate professor in 1967 and granted both a full professorship and directorship of the Clinical Microbiology Laboratories in 1972.

From 1977 through 1980 and again from 1992 until 1995, when he retired, Vosti was associate dean for student affairs. Between 1984 and 1991 he was Stanford University's associate ombudsman.

A careful scientist

Vosti was a careful scientist. "'Meticulous' is the word," said Gesundheit. "We once collaborated on a project in which it was necessary to hand-enter 10 data points apiece for 1,800 medical students — so, 18,000 data points in all. Ken not only did that by himself, he double-checked every data point. This, despite his failing vision."

Among Vosti's published works, Gesundheit said, are review articles written as long as 40 years ago that remain classics in internal medicine, such as "Recurrent Urinary Tract Infections," published in *JAMA* in 1975. He wrote or co-wrote more than 70 peer-reviewed publications on topics ranging from the pathogenesis of endocarditis to the pathogenesis of urinary tract infection. In addition, he published extensively in the field of medical education.

During his tenure at Stanford, Vosti sat on several department, school or medical center committees. He also held memberships in numerous national medical societies. In 1976, he served as president of one of them, the Lancefield Society of America.

Vosti's wife, Anne, also worked at Stanford, where she rose to the level of assistant dean of See VOSTI, page 7

Fitness

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said, is that a user can pretty much rely on a fitness tracker's heart rate measurements. But basing the number of doughnuts you eat on how many calories your device says you burned is a really bad idea, he said.

Heart-rate data reliable

Neither Ashley nor Shcherbina could be sure why energy-expenditure measures were so far off. Each device uses its own proprietary algorithm for calculating energy expenditure, they said. It's likely the algorithms are making assumptions that don't fit individuals very well, said Shcherbina. "All we can do is see how the devices perform against the gold-standard clinical measures," she said. "My take on this is that it's very hard to train an algorithm that would be accurate across a wide variety of people because energy expenditure is variable based on someone's fitness level, height and weight, etc." Heart rate, she said, is measured directly, whereas energy expenditure must be measured indirectly through proxy calculations.

PAUL SAKUMA

Study participants wore fitness trackers while walking or running on a treadmill and while pedaling on a stationary bicycle.

Ashley's team saw a need to make their evaluations of wearable devices open to the research community, so they created a website that shows their own data. They welcome others to upload data related to device performance at http://precision.stanford.edu.

The team is already working on the next iteration of their study, in which they are evaluating the devices while volunteers wear them as they go about a normal day, including exercising in the open, instead of walking or running on a laboratory treadmill. "In phase two," said Shcherbina, "we actually want a fully portable study. So volunteers' ECG will be portable and their energy calculation will also be done with a portable machine."

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

Other Stanford co-authors are clinical nurse specialist Heidi Salisbury, RN, MSN; clinical exercise physiologist Jeffrey Christle, PhD; Trevor Hastie, PhD, professor of statistics and of biomedical data science; and Matthew Wheeler, MD, PhD, clinical assistant professor of cardiovascular medicine. Ashley is also a member of the Stanford Cardiovascular Institute, the Stanford Child Health Research Institute and Stanford Bio-X. Hastie is a member of CHRI, Bio-X, the Stanford Cancer Institute and the Stanford Neurosciences Institute.

Stanford's departments of Medicine, of Genetics and of Biomedical Data Science supported the work. ISM

HIV

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effects of the interventions, singly and in combination, to determine what programs would be effective and cost-effective in preventing the spread of HIV among persons who inject drugs."

Cora Bernard

Margaret Brandeau

Prevention models studied

Of the prevention programs simulated in the model, the authors found that opioid agonist therapy, or OAT, was the most cost-effective. OAT replaces drugs like heroin with a prescription that provides similar effects under safer conditions. Methadone and buprenorphine maintenance therapies are the most common.

Needle-syringe exchange programs, in which people swap their dirty needles for clean ones, were the next most cost-effective option. This was followed by test-and-treat programs, which identify people with a high risk of contracting HIV, test them for the virus and treat them before the disease has much chance to spread — both within their own bodies and to others who are exposed.

The study estimated that PrEP can also successfully reduce HIV, but not in a cost-effective way. The authors write that the other three techniques could all cost less than $50,000 for each quality-adjusted life year gained by individuals. PrEP would likely cost more than $600,000 per quality-adjusted life year.

The prevention programs were most effective when used in combination. The authors project that combining OAT and needle-syringe exchanges could avert up to 40,000 HIV infections over 20 years among people who inject drugs, not to mention preventing downstream sexual transmission of HIV to others in the population.

According to Bernard, one of the benefits of OAT in particular is that in addition to reducing the risk of HIV, it can also help people stop injecting drugs. The authors project that expanding OAT access could decrease the size of the injection population by up to 23 percent over 20 years for low-coverage expansions and up to 37 percent over 20 years for more extensive program expansions.

OAT 'highest-value investment'

"We started out thinking about this as an HIV problem, but we realized that the majority of health benefits actually comes from reducing injection drug use and improving quality of life for drug users," said Bernard. "This is why we found OAT to be the highest-value investment."

Bernard and her co-authors believe that employing techniques like OAT could help reduce the effects of the opioid crisis.

"Our study aims to help policymakers and clinicians understand how a variety of interventions can help improve health outcomes and prevent HIV," said study co-author Douglas Owens, MD, professor of medicine and internist at the Veterans Affairs Palo Alto Health Care System. "We hope our analyses help show how to use limited resources efficiently to prevent the devastating consequences of substance use."

The study's other co-author was Jeremy Goldhaber-Fiebert, PhD, associate professor of medicine.

The work was supported by the National Institute on Drug Abuse and the Department of Veterans Affairs.

This work was also supported by the departments of Management Science and Engineering and of Medicine and by Stanford Health Policy. ISM

Population Health Sciences awards grants to 11 projects

The Stanford Center for Population Sciences has funded 11 additional pilot projects in 2017, bringing the year's total to 16. These grants support investigators whose work aims to improve the health of populations through health care system-based or community-based studies.

The grant-receiving projects and their principal investigators are:

Population health sciences

• "Design and development of a personal environmental exposure monitoring device" — Michael Snyder, PhD, professor of genetics.

• "Assessment of statins in understudied races and ethnicities" — Latha Palaniappan, MD, clinical professor of medicine.

• "Living laboratories in institutional food settings: Building a research model to help develop strategies for improving healthy food choices" — Christopher Gardner, PhD, professor of medicine.

• "Improving personalized medicine through n-of-1 causal inference and predictive modeling" — Eric Daza, DrPH, postdoctoral scholar in heart disease prevention.

• "GapMap: A mobile surveillance system to map autism and gaps in autism services globally" — Dennis Wall, PhD, associate professor of pediatrics.

• "Quantifying individual genetic risk in diverse populations" — Laramie Duncan, PhD, instructor of psychiatry and behavioral sciences.

• "Assay development for the study of skin flora and allergy in infants" — Julie Parsonnet, MD, professor of medicine and of health research and policy.

• "Telomere length changes as a marker of chronic disease risk among children participating in lifestyle behavior change" — Thomas Robinson, MD, MPH, professor of pediatrics and of medicine.

Community engagement

• "Pediatrics and education: A transdisciplinary approach to improve school readiness" — Lisa Chamberlain, MD, MPH, associate professor of pediatrics.

• "Improving food insecurity screening and referral to healthy food resources in a community clinic population in San Mateo County" — Michelle Hauser, MD, postdoctoral scholar, and Christopher Gardner, PhD, professor of medicine.

• "Developing and evaluating a K-drama precision mental health curriculum among Asian Americans and Pacific Islanders" — Van Ta Park, PhD, MPH, associate professor of health science and recreation at San Jose State University, and Mildred Cho, PhD, professor of pediatrics.

These pilot grants are administered by Spectrum (the Stanford Center for Clinical and Translational Research and Education) and the Stanford Center for Population Health Sciences. Primary funding comes from Spectrum's $45.3 million Clinical and Translational Science Award (grant UL1TR001085) from the National Institutes of Health.

The proposal deadline for next year's Spectrum pilot grants will be late in 2017. For more information, visit https://spectrum.stanford.edu. ISM

Vosti

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the university's Department of Undergraduate Admissions. After retiring, Gesundheit said, Vosti unfailingly attended biweekly meetings of the medical school's curriculum committee, on which he served pro bono for 20 years. Vosti's visual problem precluded his driving, so Anne drove him to the meetings and back.

"He never missed a meeting," said Gesundheit.

He almost never missed a Stanford basketball game, either, he added.

He was also a fan of Stanford football, said his daughter LeeAnn McDermott.

In addition to his wife and McDermott, Vosti is survived by daughters Laura Tauscher, Caroline Kohn and Aimee Lehr; brother Gordon Vosti; and 11 grandchildren.

A celebration of Vosti's life will be held at 3 p.m. today at St. Mark's Episcopal Church, 600 Colorado Ave., in Palo Alto.

His family requests that in lieu of flowers, individual donors direct their gifts to causes they favor. ISM

Lemur

continued from page 1

lemurs have great potential for our understanding of primate biology, behavior and conservation, in the same way that fruit flies and mice over the last 30 or 40 years have transformed our understanding of developmental biology and many other areas of biology and medicine," Krasnow said. "Some of the most fascinating and important questions that need to be answered are primate-specific. For those, we really need something besides humans to complement the work that has been done in fruit flies and mice."

A paper describing the researchers' findings were published online June 9 in *Genetics*. Krasnow is the senior author. Lead authorship is shared by graduate student Camille Ezran and postdoctoral scholar Caitlin Karanewsky.

The project began in 2009 when Krasnow, frustrated by the lack of a good animal model for lung disease — his area of expertise — commissioned three high school interns to search the animal world for something better. By the end of the summer, the interns had come up with the mouse lemur, which fits all the necessary criteria: Like mice, these animals are small (about twice the size of a mouse), develop quickly, reproduce rapidly, produce many offspring, and are inexpensive and easy to maintain and manage. In genetic terms, the mouse lemur is about midway between humans and mice, Krasnow said.

"When I talk to scientists, their faces light up when I tell them about mouse lemurs because they are about the size of a mouse but they are primates, so that makes a huge difference," said Ezran, who was one of the high school interns. "I think they really do present such great potential for biological, behavioral and medical research in general."

Early on in the project, Krasnow sought out the perspective of Stanford veterinarians, ultimately recruiting Megan Albertelli, DVM, PhD, assistant professor of comparative medicine. A geneticist and primate specialist, Albertelli said she was initially skeptical of the idea of lemurs as animal models, but soon became enthusiastic after realizing their enormous potential for contributions in understanding neurologic problems, eye disease and other conditions where mouse models have fallen short.

Trip to France

She accompanied the group on a trip to France to visit with scientists who had been studying lemurs in the laboratory for years. A French team had found that some aging lemurs develop a form of dementia and accumulate plaques in the brain that resemble those of Alzheimer's patients.

"I saw that they were promising models for Alzheimer's disease," Albertelli said. "Alzheimer's is a condition that is hard to model in other animal species, so that was very exciting."

Mouse lemurs live exclusively on Madagascar, where they are found in great abundance. Tens of millions of them populate the island. While lemurs generally are endangered due to habitat destruction, mouse lemurs are not under threat and freely roam the island, said Ezran, who calls them the "rodents of Madagascar."

The Stanford researchers began to develop collaborations with other scientists studying lemurs, including those at the Centre ValBio near the Ranomafana National Park in Madagascar, who have been examining lemur ecology, family structure and behavior for decades.

During periodic visits to the island, Krasnow and his colleagues learned how to catch brown mouse lemurs in the rainforest just outside the research station, using a tiny banana slice inside a trap as a lure. The scientists then tagged and photographed each animal, gave them a thorough physical examination, analyzed them for behavioral issues and abnormalities and removed a drop of blood for detailed genetic and serum studies. The animals then were released back into the wild so the researchers could follow them over time to see how their environments may influence their progress and health. In 2013, Stanford built a sophisticated molecular biology and genetics lab within the ValBio complex, where these studies could be carried out.

Distinctive personalities

Lemurs have distinctive personalities, Krasnow said, and the researchers gave each one a name, based on his or her looks or behavior. For instance, one was named Feisty for his unusually aggressive nature; most lemurs are docile.

The work has led to a whole new way of doing genetic studies, said Krasnow, who is also a Howard Hughes Medical Institute investigator. Instead of using the traditional method of introducing genetic mutations into mice to create "knockout" mice — or animals with customized genes — they found they were able to find naturally occurring variants among animals in the wild. Moreover, in working with lemurs in their native habitats, the researchers could better understand how the animals interact with their surroundings and the relationship between genes and the environment.

Mark Krasnow

"Instead of introducing mutations in mice or fruit flies, we are doing something much more similar to what is done in humans," he said. "We are looking at all the wonderful genetic variation already existing in nature, since there are so many millions of mouse lemurs out there. We calculate that most 'knockout' mutations are already present in nature, and all we have to do is find them. And because the cost of sequencing a genome is rapidly dropping, it's now possible to sequence the genomes of thousands of mouse lemurs to see what mutations they are carrying."

In doing so, the researchers could accomplish in a few years for a tiny fraction of the cost what the International Knockout Mouse Consortium will accomplish in 10 years, at a cost of nearly $1 billion, he said.

But the project could use some additional staff, as the process of capturing the animals and screening them in the laboratory is labor-intensive, he said. He and his colleagues have come up with a multipurpose solution that will contribute to the local educational system while helping preserve the lemur populations in Madagascar, whose habitats are threatened by farming, mining and logging interests, he said.

Help from students

The group is developing a science curriculum for use in Malagasy high schools in which students learn about biology by exploring the rich environment right outside their school houses. Among the instructors is Manu Prakash, PhD, assistant professor of bioengineering at Stanford and a pioneer in the field of "frugal science," who has brought his powerful $1 paper microscopes to Madagascar and taught students how to explore the microscopic world in which they live, including the lice in their hair, the pathogens in their water and the disease-causing parasites in their environment. The curriculum was first introduced among university students, some of whom now are screening lemurs at the Stanford lab in Madagascar.

"We saw this as an opportunity because we are going over there to study the unique animals and biology and ecology of Madagascar, which is unsurpassed in the world," Krasnow said. "It is the No. 1 hotspot for biodiversity, but most of the students don't realize what they have in their backyards because they are being taught from textbooks and from teachers who have learned from Europeans."

He said the researchers hope to expand scientific curricula at all levels of education, helping train the Malagasy scientists of the future and build scientific capacity in the country, all the while creating an appreciation among the local population of the need to understand and preserve lemurs and other species for the future.

"We are trying to do this in a way that is respectful and will help the lemurs and the people of Madagascar, while enlightening many aspects of primate biology and human disease," he said.

The researchers plan to make the genetic sequencing and phenotyping information they obtain from the lemurs publicly available so that researchers around the world can take advantage of this trove of knowledge, Albertelli said.

Other Stanford co-authors are graduate students Maya Krasnow and Stephan Chang, former undergraduate student Jason Willick, former research assistant Alexander Sholtz and lab technician Jozeph Pendleton. (Maya Krasnow and Willick are two of the former high school interns who began work on the project in 2009.)

Researchers at the University of Antananarivo and Auburn University also co-authored the study.

The research was supported by the Howard Hughes Medical Institute and the Vera Moulton Wall Center of Stanford University.

Stanford's Department of Biochemistry also supported the work. ISM

Nancy Morioka-Douglas wins professionalism award

Nancy Morioka-Douglas, MD, clinical professor of medicine, has received the Dr. Augustus A. White and Family Faculty Professionalism Award.

The honor recognizes outstanding work in reducing health disparities or in enhancing the effectiveness of underrepresented minorities in the university community through research, education, mentoring or service.

Morioka-Douglas was honored for her work developing service-learning opportunities for medical trainees. Most recently, she creating an initiative that allows family medicine residents to train high school students from low-income minority communities to serve as diabetes self-management coaches for family members. The program is now in use at 11 medical institutions and 17 high schools in the United States and Canada.

The award is given in odd years and includes $1,500. Its namesake, White, was the first African-American graduate of the School of Medicine in 1961. ISM

STEVE FISCH

Nancy Morioka-Douglas (right) receives the award from Yvonne Maldonado, senior associate dean for faculty development and diversity, and Augustus White, the alumnus for whom the award is named.

OF NOTE

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

BEN BARRES, MD, PhD, professor of neurobiology, of developmental biology and of neurology and neurological sciences, has received a 2017 President's Award for Excellence Through Diversity from Stanford University. The honor recognizes individuals and programs that have made exceptional contributions to enhance and support diversity on campus. Barres was honored "for blazing trails as a brilliant scholar and researcher, exceptional teacher, academic leader and as the first transgender man elected to the National Academy of Sciences."

CATHERINE BLISH, MD, PhD, assistant professor of medicine, was named a 2017 Investigator in the Pathogenesis of Infectious Disease by the Burroughs Wellcome Fund. The program provides $500,000 over five years to investigate the interactions between microbes and humans. Blish will use her award to understand how natural killer cells fight HIV infection.

ANNA DAPELO-GARCIA, administrative director of patient access services for Stanford Health Care, was named the 2017 Woman of the Year by Woman Health Care Executives of Northern California. The honor recognizes a woman whose leadership and contributions to the health care field are exceptional and deserving of recognition. She founded Lean In Latinas and is a regional program leader of Lean In, an organization that provides networking opportunities and career support for women.

MICHAEL FISCHBACH, PhD, was appointed associate professor of bioengineering, effective April 1. His research uses techniques from genomics and chemistry to analyze small molecules from the human microbiome.

NEIL GESUNDHEIT, MD, professor of medicine and an associate dean for academic advising, was given the RISE Award by the Stanford Medicine Alumni Association. The honor recognizes an individual who represents the organization's values to reach, inspire, serve and engage Stanford medical students, residents and alumni and who has demonstrated an exceptional dedication to nurturing Stanford Medicine and the alumni community.

MICHAEL GISONDI, MD, was appointed associate professor of emergency medicine, effective May 1. He is the vice chair of education for emergency medicine. His scholarly interests include medical education research and faculty development.

KEREN HAROUSH, PhD, was appointed assistant professor of neurobiology, effective April 1. Her research focuses on the neuronal circuits that drive social interactions.

KELLEY HARRIS, a postdoctoral scholar in genetics, received a 2016 Editors' Choice Award in Population Genetics from the Genetics Society of America for the paper "The Genetic Cost of Neanderthal Introgression," of which she was lead author. The paper appeared in June in the journal *Genetics*.

RAVI MAJETI, MD, PhD, associate professor of medicine, has been named the division chief of hematology in the Department of Medicine. His research focuses on the molecular and genomic characterization and targeting of leukemia stem cells.

KARIM SALLAM, MD, clinical instructor of medicine, was awarded the William W. Parmley Young Author Achievement Award by the American College of Cardiology. The honor recognizes two outstanding papers published in the *Journal of the American College of Cardiology* by lead authors who are within five years of completing their training requirements for a specialty board certification or PhD. Sallam was recognized for "Patient-specific and genome-edited induced pluripotent stem cell-derived cardiomyocytes elucidate single-cell phenotype of Brugada syndrome."

DAVID SCHNEIDER, PhD, was promoted to professor of microbiology and immunology, effective March 1. He is chair of the department. His research interests include innate immunity, microbial pathogenesis and the progress of and recovery from infections.

LESLEE SUBAK, MD, was appointed professor of obstetrics and gynecology, effective May 1. She is the chair of the department. She specializes in urogynecology and pelvic surgery and conducts research on urinary incontinence in women.

THOMAS SÜDHOF, MD, professor of molecular and cellular physiology, has been elected a fellow of the Royal Society, the independent scientific academy of the United Kingdom, which includes distinguished scientists from all areas of science, engineering and medicine. He is one of 10 foreign members selected this year. Südhof was awarded the 2013 Nobel Prize in Physiology or Medicine for his discoveries of machinery regulating vesicle traffic, a major cellular transport system. He holds the Avram Goldstein Professorship.

MINTU TURAKHIA, MD, was promoted to associate professor of medicine, effective April 1. He is the director of cardiac electrophysiology at the Veterans Affairs Palo Alto Health Care System and senior director of the Stanford Center for Digital Health. His research focuses on improving the treatment of heart-rhythm disorders using methods that range from health-services research to multicenter clinical trials of technological interventions. Turakhia recently received a $200,000, two-year grant from the American Heart Association and Amazon Web Services to use artificial intelligence methods to improve clinical decision-making for stroke prevention in atrial fibrillation.

PAUL WANG, MD, professor of medicine, was named the editor-in-chief of *Circulation: Arrhythmia and Electrophysiology*, a journal published by the American Heart Association. Wang is the director of the hospital's cardiac arrhythmia service, co-director of the Stanford Center for Arrhythmia Research and a faculty liaison for the Stanford Byers Center for Biodesign.

JOSEPH C. WU, MD, PhD, professor of medicine and of radiology, has been given a $1 million Merit Award from the American Heart Association. The award is intended to advance cardiovascular precision health. Wu plans to use patient- and disease-specific induced pluripotent stem cells to select optimal drugs for individual patients and to accelerate drug discovery using the concept of "clinical trial in a dish." He is the director of the Stanford Cardiovascular Institute and the Simon H. Stertzer, MD, Professor.

FAN YANG, PhD, was promoted to associate professor of orthopaedic surgery and of bioengineering, effective June 1. In addition, she has received the Ellen Weaver Award for Outstanding Mentoring from the Association for Women in Science-Northern California Chapters. The award is given to a woman early in her career who has combined scientific achievement and mentoring, with demonstrated commitment to mentoring and support of other women in science. Yang's research focuses on developing biomaterials and cell-based therapies for treating diseases including musculoskeletal disorders, cardiovascular diseases and cancer. ISM

Ben Barres

Catherine Blish

Anna Dapelo-Garcia

Michael Fischbach

Neil Gesundheit

Michael Gisondi

Ravi Majeti

Karim Sallam

David Schneider

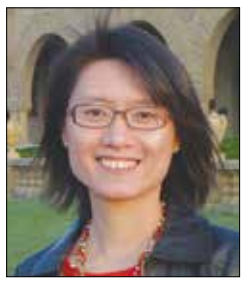
Leslee Subak

Thomas Südhof

Mintu Turakhia

Paul Wang

Joseph C. Wu



Fan Yang