INSIDE STANFORD MEDICINE

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Speakers at a daylong symposium discussed ways to improve electronic health records.
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Blood test can predict premature birth

By Erin Digitale

A new blood test for pregnant women detects with 75-80 percent accuracy whether their pregnancies will end in premature birth. The technique can also be used to estimate the gestational age of a fetus — or the mother's due date — as reliably as and less expensively than ultrasound.

Developed by a team of scientists led by researchers at Stanford University, the tests could help reduce problems related to premature birth, which affects 15 million infants worldwide each year. Until now, doctors have lacked a reliable way to predict whether pregnancies will end prematurely, and have struggled to accurately predict delivery dates for all types of pregnancies, especially in low-resource settings.

The blood tests are described in a paper that was published online June 7 in *Science*. Stephen Quake, PhD, professor of bioengineering and of applied physics at Stanford, shares senior authorship with Mads Melbye, MD, visiting professor of medicine. The lead authors are former Stanford postdoctoral scholar Thuy Ngo, PhD, and Stanford graduate student Mira Moufarrej.

"This work is the result of a fantastic collaboration between researchers around the world," said Quake, who is also the Lee Otterson Professor in the School of Engineering. "We have worked closely with the team at the Stanford March of Dimes Prematurity Research Center, and the research involved collaborations with scientists in Denmark, Pennsylvania and Alabama. It's really team science at its finest."

The tests measure the activity of maternal, placental and fetal genes by assessing maternal blood levels of cell-free RNA, tiny bits of the messenger molecule that carry the body's genetic instructions to its protein-making factories. The team used blood samples collected during pregnancy to identify which genes gave reliable signals about gestational age and prematurity risk.

"We found that a handful of genes are very highly predictive of which women are at risk for preterm delivery," said Melbye, who is also president and CEO of the Statens Serum Institut in Copenhagen. "I've spent a lot of time over the years working to understand preterm delivery. This is the first real, significant scientific progress on this problem in a long time."

JOEL SIMON IMAGES

Stephen Quake collaborated with other researchers to develop a blood test that gives a reliable estimate of a baby's due date and can predict preterm birth.

Toll of preterm births

Premature birth, in which a baby arrives at least three weeks early, affects 9 percent of U.S. births. It is the largest cause of infant mortality in the United States and the largest contributor to death before age 5 among children worldwide. In two-thirds of preterm births, the mother goes into labor spontaneously; doctors usually do not know why. Previously, the best available tests for predicting premature birth worked only in high-risk women, such as those who had already given birth prematurely, and were correct only about 20 percent of the time.

Quake first took an interest in this problem when he became a parent: His daughter was born nearly a month early. "She's now a very healthy and active 16-year-old, but it certainly stuck in my mind that this is an important problem to work on," Quake said.

Doctors also need better methods for measuring gestational age, he added. Obstetricians now use ultrasound scans from the first trimester of pregnancy to estimate a woman's See TEST, page 6

Compound found in citrus oil could reduce dry mouth in head, neck cancer patients

By Becky Bach

A compound found in citrus oils could help alleviate dry mouth caused by radiation therapy in head and neck cancer patients, according to a new study by researchers at the School of Medicine.

The compound, called d-limonene, protected cells that produce saliva in mice exposed to radiation therapy — without diminishing the tumor-fighting effects of the radiation. The researchers, led by graduate student Julie Saiki, also showed that taken orally, d-limonene is transported to the salivary gland in humans.

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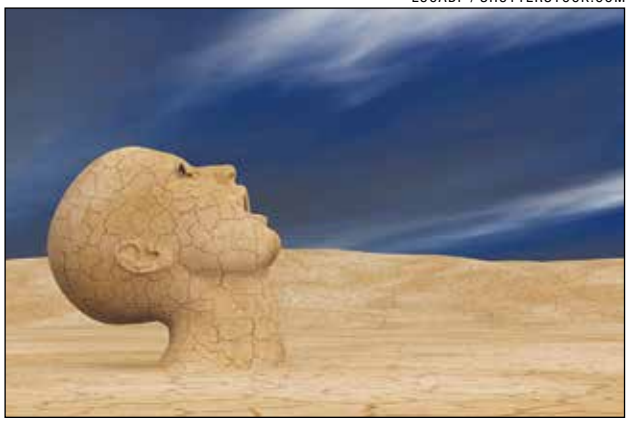

The study was published online May 21 in the *Proceedings of the National Academy of Sciences*.

The finding was possible because of a close collaboration between clinicians and basic scientists, said co-senior author Daria Mochly-Rosen, PhD, professor of chemical and systems biology. "This is a perfect example of two pieces that could not work alone."

"Stanford is a fertile ground for collaboration," added Quynh-Thu Le, co-senior author and professor and chair of radiation oncology.

About 40 percent of head and neck cancer patients who receive radiation therapy develop dry mouth, known clinically as xerostomia. It's more than uncomfortable: Patients struggle to speak and swallow and are more likely to develop oral pain or dental cavities, and the condition can lead to tooth removal, in some cases, Le said. And, although some recovery can occur in the first years after the therapy, once saliva production is impaired, it is usually gone for life.

Radiation can kill salivary cells

One drug, called amifostine, is approved for use during radiation therapy to try See DRY, page 7

Blood cells transformed into functional neurons

By Krista Conger

Marius Wernig

Human immune cells in blood can be converted directly into functional neurons in the laboratory in about three weeks with the addition of just four proteins, researchers at the School of Medicine have found.

The dramatic transformation does not require the cells to first enter a state called pluripotency but instead occurs through a more direct process called transdifferentiation.

The conversion occurs with relatively high efficiency — generating as many as 50,000 neurons from 1 milliliter of blood — and it can be achieved with fresh or previously frozen and stored blood samples, which vastly enhances opportunities for the study of neurological disorders such as schizophrenia and autism.

"Blood is one of the easiest biological samples to obtain," said Marius Wernig, MD, associate professor of pathology and a member of Stanford's Institute for Stem Cell Biology and Regenerative Medicine. "Nearly every patient who walks into a See NEURONS, page 6

Study identifies cell 'death code,' a microscopic Grim Reaper

By Hanae Armitage

Dying cells generally have two options: go quietly, or go out with a bang.

The latter, while more conspicuous, is also mechanistically more mysterious. Now, scientists at the School of Medicine have pinpointed what they believe is the molecular "code" that unleashes this more violent variety of cell death.

This particular version of cell suicide is called necroptosis, and it typically occurs as a result of some sort of infection or pathogenic invader. "Necroptosis is sort of like the cell's version of 'taking one for the team,'" said Jan Carette, PhD, assistant professor of microbiology and immunology. "As the cell dies, it releases its contents, including a damage signal that lets other cells know there's a problem."

Seen in this light, necroptosis seems almost altruistic, but the process is also a key contributor to autoimmune diseases; it's even been implicated in the spread of cancer.

In a new study, Carette and his collaborators discovered the final step of necroptosis, the linchpin upon which the entire process depends. They call it "the death code."

Their work, which was published online June 7 in *Molecular Cell*, not only clears up what happens during this type of cell death, but also opens the door to potential new treatments for diseases in which necroptosis plays a key role, such as inflammatory bowel disease and multiple sclerosis. Carette is the senior author, and postdoctoral scholar Cole Dovey, PhD, is the lead author.

PAUL SAKUMA

Jan Carette is the senior author of a study describing the final, crucial step in a type of cell death called necroptosis, which typically occurs as a result of some sort of infection or pathogenic invader.

Initiating detonation

When a cell's health is threatened by an invader, such as a virus, a cascade of molecular switches and triggers readies the cell for death by necroptosis. Until recently, scientists thought they had traced the pathway down to the last step. But it turns out that the entire chain is rendered futile without one special molecule, called inositol hexakisphosphate, or IP6, which is part of a larger collection of molecules known as inositol phosphates. Carette likens IP6 to an access code; only in this case, when the code is punched in, it's not a safe or a cellphone that's unlocked: It's cell death. Specifically, a protein called MLKL, which Carette has nicknamed "the executioner protein," is unlocked.

"This was a big surprise. We didn't know that the killer protein required a code, and now we find that it does," Dovey said. "It's held in check by a code, and it's released by a code. So only when the code is correct does the killer activate, puncturing holes in the cell's membrane as it prepares to burst the cell open."

MLKL resides inside the cell, which may seem like an error on evolution's part; why plant an explosive in life's inner sanctum? But MLKL is tightly regulated, and it requires multiple green lights before it's cleared to pulverize. Even if all other proteins and signaling molecules prepare MLKL for destruction, IP6 has the final say. If IP6 doesn't bind, MLKL remains harmless, like a cotton ball floating inside the cell.

When it's not killing cells, MLKL exists as multiple units, separate from one another. But when IP6 binds to one of these units, the protein gathers itself up into one functional complex. Only then, as a whole, is MLKL a full-fledged killer. It's like a grenade split into its component parts. None of them are functional on their own. But put back together, the tiny bomb is ready to inflict damage.

> "Only when the code is correct does the killer activate."

"We've come to realize that after the cell explodes, there are these 'alarm' molecules that alert the immune system," Dovey said. "When the cell releases its contents, other cells pick up on these cautionary molecules and can either shore up defenses or prepare for necroptosis themselves."

Screening for the Grim Reaper

In their quest to understand exactly how necroptosis occurs, Carette and Dovey performed an unbiased genetic screen, in which they scoured the entire genome for genes that seemed to be particularly critical toward the end of the pathway, where they knew MLKL took action. Before the IP6 finding, it was known that an intricate pathway impinged on MLKL. But only through this special genetic screen, in which they systematically tested the function of every gene at this end stage, were they able to see that IP6 was the key to necroptosis.

"Genetic screens are a lot of fun because you never know what you're going to get," Carette said. "We feel quite excited that we've been able to pinpoint IP6."

Their screen revealed that IP6 binds with especially high specificity. Other similar versions of inositol phosphate, such as IP3, didn't pass muster, and when bound to MLKL had no effect. This gave Carette an interesting idea. For conditions like irritable bowel disease, in which erroneous necroptosis contributes to the severity of the disease, it would be desirable to disable IP6 from binding under those conditions. Perhaps blocking the binding site, or tricking MLKL into binding to one of the other versions of inositol phosphate, could do the trick. Either way, Carette and his collaborators are now digging further into the structure of IP6 bound to MLKL to better understand exactly how the killer is unleashed.

"In terms of drug discovery, inositol phosphates have been somewhat ignored, so we're really excited to be able to look into these small molecules for potential therapeutic reasons," Carette said.

Other Stanford co-authors on the study are graduate student Jonathan Diep; postdoctoral scholar Jennifer Yinuo Cao, PhD; and assistant professor of biology Scott Dixon, PhD.

Carette is a member of Stanford Bio-X and the Stanford Child Health Research Institute.

Researchers at Vanderbilt University, St. Jude Children's Research Hospital, the University of Texas, Princeton University, Leibniz-Forschungsinstitut für Molekulare Pharmakologie, GlaxoSmithKline and Emory University also contributed to the work.

The study was supported by the National Institutes of Health, the David and Lucile Packard Foundation, St. Jude Children's Research Hospital and the American Lebanese Syrian Associated Charities, the fundraising organization for St. Jude.

Stanford's Department of Microbiology and Immunology also supported the work. **ISM**

$2.5 million award to support physician-scientist training

Stanford has been selected as one of five universities to receive a Physician Scientist Institutional Award from the Burroughs Wellcome Fund. The grant, announced June 1, provides the School of Medicine with $2.5 million over five years to support novel programs that enhance career development for medical students who wish to strengthen their research skills.

Physician-scientists are essential bridges between clinics and labs, and are defined as physicians who spend a majority of their time conducting research. Most physician-scientists hold both an MD and PhD. The grant is designed to encourage research among the group of nearly 20,000 MD-only physicians who graduate annually from medical schools in the United States.

PJ Utz

Medical students at Stanford are required to complete a scholarly concentration to graduate, and many want to pursue longer-term research projects by spending an extra year on campus.

With funding from the award, Stanford will take this five-year curriculum a step further, allowing students to add a sixth year of full-time research as a Burroughs Wellcome Fund Scholar, said PJ Utz, MD, professor of medicine and associate dean of medical student research, who is also one of the three principal investigators for the grant.

The grant, together with financial commitments from the school's Medical Scholars Program and the Dean's Office, will help fund students' research in years 2 and 3, and will fully fund research and clinical clerkships during the last three years of training. As many as five students per year will be recruited, with a goal of matching the students to research-intensive residencies at top-tier programs. Utz said an effort is underway to develop an associated master's degree in the biosciences at Stanford for MD students.

"In addition to our outstanding, almost 50-year-old MD-PhD program, our new Burroughs Wellcome Fund Scholars Program will generate MD-only physician-scientists who are curious, outstanding researchers and caring clinicians," Utz said. "They will take questions from their patients back to their research groups to figure out solutions to unsolved problems."

Utz said he is stepping down as director of Stanford's MD-PhD program to direct the new Burroughs Wellcome Fund Scholars Program. His fellow principal investigators for the grant are Nobel laureates Paul Berg, PhD, professor emeritus of biochemistry, and Brian Kobilka, MD, professor of molecular and cellular physiology. **ISM**

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STANFORD MEDICINE

Four recipients of Spirit, Inspiring Change awards announced

By Kris Newby

The School of Medicine has announced the winners of the annual Anne G. Crowe Spirit Award and 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 Misty Mazzara, an educational program manager in the Department of Health Research Policy, and Michela Pilo, an administrative associate in the Department of Dermatology.

The Inspiring Change Leadership Award, which goes to staff members who have implemented processes that improve the school, was given to both Kim Osborn, administrative director of clinical education in School of Medicine Student Affairs, and Shannon Monahan, a research analyst in the Office of Postdoctoral Affairs.

Each winner receives $3,000.

Misty Mazzara

With gusto and pizzazz, Misty Mazzara manages the four graduate-level educational programs in the Department of Health Research and Policy. In this role, she juggles the tasks associated with admissions, orientation and graduation for the master of science and PhD degree programs in epidemiology and clinical research and in health policy. She also assists these graduate students in tracking course requirements, applying for scholarships and finding paid research positions.

"Misty is incredibly helpful in guiding students through the graduate program application process and tracking the myriad details necessary for completing the degrees," said Martha Kessler, executive director of finance and administration in health research and policy and several other units at the medical school.

Mazzara started at Stanford in the Department of Medicine in 2012, after spending a decade traveling the world with her daughter and husband, a Navy pilot. She said this experience contributed to her resilience and resourcefulness.

After her husband left the military to enroll in Stanford Law School's JD-MBA program, she jumped at the chance to launch a career in higher education.

"I figured I'm down the street from the best university in the world, and I'd love the opportunity to work there," she said.

In June 2016, she joined the health research and policy team and began streamlining the administrative processes and launching the new PhD program in epidemiology and clinical research. As she has settled into her role as educational program manager, she has also been taking advantage of the many educational opportunities available to Stanford employees, including management training classes and kickboxing.

"Misty's dedicated service, initiative, thoughtfulness and positive attitude are truly appreciated by everyone, and she has consistently demonstrated all the qualities this Spirit Award intends to recognize and honor," said Rita Popat, PhD, clinical associate professor of health research and policy.

Michela Pilo

The most amazing office administrators combine all the best qualities of air traffic controllers, Walmart greeters, computer troubleshooters and clairvoyants. They keep the office humming and happy.

Michela Pilo, the senior administrative associate in the Department of Dermatology, is just such an administrator, and because of this, her department nominated her for a spirit award.

"She goes above and beyond every day to ensure the success of the department, anticipating problems and intervening before they become issues," said Justin Ko, MD, MBA, clinical associate professor of dermatology.

Sumaira Aasi, MD, clinical professor of dermatology, said, "Michela is tenacious and does not give up until she has explored every option and found a solution. She doesn't see the boundaries of her job description, but rather looks for opportunities that allow those around her to work more efficiently. The department is fortunate to have someone whose spirit and work ethic inspires others."

One of the things Pilo likes about her job is that every day is different. On a daily basis she manages complex executive calendars and the schedules of her 40-plus dermatology faculty and researchers. She makes sure supplies never run out. She solves technical problems with the computer-based systems. She keeps the office neat.

She also likes her co-workers. "There are very smart, humble people here, and it's hard not to love working with them," she said.

Before Pilo moved to Stanford four years ago, she worked for 12 years as a jack-of-all-trades at a nonprofit arts foundation. The thing she appreciates about her current position is its healthy work-life balance, which has allowed her to spend more time with her husband and two teenagers, as well as indulge in her passion for Italian cooking.

"Michela is an exemplary department representative, focused on service both inside and outside of Stanford," said Tyler Hollmig, MD, clinical associate professor of dermatology. "She is so efficient — seemingly does the work of a multitude. And she does it with a smile on her face and a generous spirit."

Kim Osborn

Kim Osborn was instrumental in the launch of an innovative new course that provides first-year medical students with early patient experience, and this is one of the many reasons she was awarded an Inspiring Change Leadership Award. The course, called "Walk With Me: A Patient-Centered Exploration of Health and the Health Care System," pairs medical students with patients and their families to jointly explore health-related topics through a series of workshops. Students and patient partners also meet monthly outside of the classroom in clinical and nonclinical settings.

"She's the most creative, supportive, innovative and effective administrative partner that I've ever worked with," said Erika Schillinger, MD, clinical professor of primary care and population health and director of the Stanford Healthcare Innovations and Experiential Learning Directive. "She is always looking for opportunities to align our work with the broader missions of Stanford, and it is a joy to craft programs with her. The 'Walk With Me' course is an example: We are now building human connections between caregivers, medical students, physician-assistants and patients from the first days of medical student training."

Schillinger is also impressed with Osborn's workplace-culture-building skills: "She respects all members of her team and is always looking for ways to move the team forward together."

When asked about what she likes best about working at Stanford, Osborn said, "I enjoy making broad impacts, finding innovative ways to add value and removing barriers to progress for a variety of customers. This often requires building relationships across institutions."

On a personal level, Osborn appreciates the university's many opportunities for career growth. "With management and faculty support, I was able to earn a master's in public administration and contribute to academic presentations and publications. These experiences over the last eight years have expanded my perspective on the value of staff at Stanford."

Shannon Monahan

Shannon Monahan won an Inspiring Change Leadership Award for her dedication to continuous improvement in the systems and processes that support postdoctoral training at Stanford University.

When she joined the office in March 2006, postdoctoral scholars were appointed through a laborious paper-based process. Monahan served as the technical lead in designing an online platform that streamlined the appointment processes and enabled the collection of data that could be used to understand the postdoctoral experience at Stanford. Since that time, she has continuously advocated for improvements to the myriad systems that impact postdoctoral administration. For example, she pushed for a policy change that allowed postdoctoral registration fees to be automatically charged to applicable projects. This saved hundreds of hours of administrative work each year over all the schools and eliminated the surprise collection notices delivered to postdocs who were unaware of the erroneous bills. She also helped guide the redesign of the graduate financial system, a platform which now features a separate module for paying postdocs.

"Monahan's analytical talents, attention to detail, understanding of arcane systems and ability to work with a wide range of people have made her an immeasurably effective change agent," said Sofie Kleppner, PhD, associate dean for postdoctoral affairs.

"My goal has always been to put myself out of a job by automating things," said Monahan. "If I can get systems to a point where my colleagues can access the data that they need anytime and anywhere, that'd be terrific."

She was also instrumental in the establishment and administration of a hardship fund for postdoctoral scholars, which covers expenses such as housing and child care for postdocs. Her analyses were invaluable in modeling the impact of the recent increase in the minimum postdoctoral salary to $60,000, as was recently announced by the provost.

"Through her outstanding ability and remarkable dedication, Shannon has generated and analyzed the data supporting the efforts of university leadership and the faculty to provide the best possible environment for postdoctoral training," said Will Talbot, PhD, senior associate dean for graduate education and postdoctoral affairs. "Her deep knowledge and thoughtful approach have been recognized by the National Science Foundation, which has consulted with her on its surveys and panel discussions."

"In an institution that values data, information, continuous improvement and collaboration, Monahan sets a unique and powerful standard," Kleppner said.

Monahan attributes her success, at least in part, to the work ethic that her parents instilled in her while growing up on the Jersey Shore. She plans to use the award money for a trip to Ireland to visit her ancestral homeland and meet a few long-lost relatives. **ISM**

KRIS NEWBY

(From left) Michela Pilo, Kim Osborn, Misty Mazzara and Shannon Monahan were honored for outstanding service to the medical school.

Experts discuss ways to improve electronic health records

By Amy Jeter Hansen

A Stanford Medicine survey conducted by The Harris Poll found that more than 6 in 10 primary care doctors say electronic health records have led to improved patient care. However, a majority also report frustration with how the demands of the digital systems affect their relationships with patients.

Presenting the results June 4 at Stanford Medicine's EHR National Symposium, Lloyd Minor, MD, dean of the School of Medicine, said the survey illustrates the gap between the potential and current reality of the documentation technology. He charged the attendees — leaders in patient care, technology, design thinking and public policy — to chart a future that fulfills the clinical promise of EHRs while reducing the administrative burdens.

"We absolutely don't want today to be about pointing fingers or trying to assign blame," Minor said. "The goal of today's conference is to define where we are today, identify the opportunities for the future, and begin to form a road map about how we succeed in achieving those opportunities."

With panel discussions and breakout sessions focused on problem-solving, the daylong symposium touched on fixing inefficiencies in EHRs, harnessing data for population health management, building on successes and overcoming obstacles.

The online survey — of more than 500 primary care physicians throughout the United States — provided a baseline of opinions and experiences.

What doctors report

Two-thirds of doctors report being at least somewhat satisfied with their electronic health records system, though 4 in 10 say the records bring more challenges than benefits, according to the survey. About 7 in 10 physicians say EHRs take valuable time away from patients, and an equal percentage say the systems contribute greatly to burnout.

Of 31 minutes devoted to a patient, doctors estimate they spend 12 interacting with the patient, eight interacting with the records systems during the visit, and another 11 minutes on the computer after the visit, according to the poll.

Though data entry required by digital systems can be burdensome, local culture and workflow can influence how physicians regard their EHR experience, panelists at the symposium said.

Christine Sinsky, MD, vice president of professional satisfaction at the American Medical Association, said that over 16 years, she's seen expectations for digital documentation grow. "The expectations that every act must go through the EHR, that we translate the clinical experience into digital data for the convenience of others and not for advancing clinical care — those pressures have increased."

Taylor Davis of KLAS, a company that compiles and analyzes user feedback on health information technology for vendors, said surveys with more than 20,000 respondents found that organizations with the most satisfied workers were not the ones with cutting-edge technology, but those that emphasized teamwork, training and understanding how to use the system.

"These are organizations where physicians realize that it's a myth that the [EHR] is going to be intuitive enough that I can just pick it up and use it out of the box," said Davis, a vice president of analysis and strategy at the company.

PHOTOS BY ROD SEARCEY

(Right) Lloyd Minor gave closing remarks at the Electronic Health Records National Symposium, which was held June 4 at the Li Ka Shing Center for Learning and Knowledge. (Below) *New York Times* reporter Reed Abelson (far right) moderated a panel that included Donald Rucker (middle), the national coordinator for health information technology at the U.S. Department of Health and Human Services, and Judy Murphy (left), chief nursing officer with IBM Global Healthcare.

EHRs for better care

Some organizations at the symposium reported using data gleaned from EHRs to inform and improve care. Stanford Children's Health devised a tool that collects information on cases of jaundice in premature infants to be analyzed alongside expert-based consensus to ensure best practices continue to be followed as they evolve. Intermountain Healthcare created a transportation program for Medicaid patients after an analysis of patient records revealed that a main reason they were visiting the emergency department for nonurgent care was lack of transport.

At Kaiser Permanente, Brian Hoberman, MD, said there have long been numerous opportunities for health care based on patient data, and identifying patients that need a particular service is not difficult. One challenge is prioritizing which health needs to tackle with the data. Another is addressing the occasional barrier from individual patients' lives.

"We're able to find folks who need to come in to manage their diabetes or hypertension, and we're able to actually pick them up," Hoberman said. "That doesn't necessarily mean that they're going to choose to come in, for whatever reason."

Engaging patients more actively in their care has been a major benefit of electronic health records, panelists said. Through portals created for them, patients have started participating more in decision-making and care planning, said Judy Murphy, chief nursing officer with IBM Global Healthcare. Patients are now thinking more about health care as a way of life rather than as episodic encounters, she said: "That has been a huge boon to the way we think about care in the United States."

Though some said providers and other health organizations are unlikely to invest in changes without a financial or regulatory incentive, others said patients, as consumers accustomed to the online retail experience, would drive innovations in electronic health records — particularly as they assume more of the health care risk because of developments like high-deductible insurance plans.

A big step forward is the new Apple Health Records application programming interface, said Donald Rucker, MD, the national coordinator for health information technology at the U.S. Department of Health and Human Services. The API will allow developers to create apps that can use electronic health records data to help people manage their health care, medications and more.

"Some of the more esoteric things — the machine learning, all of that — will piggyback off that broader consumer involvement, the way it does in other industries," Rucker said. **ISM**

Most trial participants favor sharing personal data for research

By Beth Duff-Brown

Most participants in clinical trials believe the benefits of broadly sharing person-level data outweigh the risks, according to a new study by Stanford University researchers.

Michelle Mello

Steven Goodman

And despite low levels of trust in pharmaceutical companies, most of those who take part in clinical trials are willing to share their data with drug firms, the researchers found.

The study was published in the June 7 issue of *The New England Journal of Medicine*. The lead author is Michelle Mello, JD, PhD, professor of law and of health research and policy. Steven Goodman, MD, PhD, professor of medicine and of health research and policy, is the senior author.

The researchers surveyed 771 current and recent participants from a diverse sample of clinical trials at three academic medical centers in the United States. They asked about the practice of making personal data collected in medical research widely available after the removal of information that could identify individual participants. Nearly 80 percent of those surveyed responded to the questions — and fewer than 8 percent of the respondents felt that the potential negative consequences of data sharing outweighed the benefits.

Some 93 percent of those surveyed said they were very or somewhat likely to allow their data be shared with university scientists, and 82 percent were either very or somewhat likely to allow their data to be share with scientists at for-profit companies. The researchers found that the willingness to share was high regardless of the purpose for which their data would be used, unless that purpose was litigation.

Although some researchers and trial funders have worried that participants might object to data-sharing as an invasion of privacy, the respondents' greatest concern was that "data sharing might make others less likely to enroll in clinical trials," the authors wrote. "Less concern was expressed about discrimination (22 percent) and exploitation of data for profit (20 percent.)"

The authors acknowledge there is no turning back from clinical data sharing.

"We are rapidly moving toward a world in which broad sharing of participant-level clinical trial data is the norm," they wrote.

Expanding access to data

Major research sponsors and journal editors have begun promoting data sharing, and the National Institutes of Health now requires its grantees to describe how they will share their data with others.

Pharmaceutical industry associations have committed to making data more accessible, and several data platforms are now available, such as the Yale Open Data Access Project.

See DATA, page 5

Conference focuses on how to make tech work for patient care

By Hanae Armitage

PHOTOS BY ROD SEARCEY

(Clockwise from top) Dean Lloyd Minor gave introductory remarks at the Big Data in Precision Health Conference, which was held at the Li Ka Shing Center for Learning and Knowledge. Computer scientist Andrew Ng discussed artificial intelligence at the conference. Carla Pugh, far left, moderated a panel on digital health and technology featuring Jennifer Schneider, Leanne Williams, Lisa Suennen and Rich Mahoney.

As vast troves of health data accumulate through wearable technologies, genome sequencing and an increased interest from patients in monitoring their own health, scientists and doctors face a challenge: how to get this data into the hands of those who need it the most — health care professionals, doctors and a growing list of researchers applying new technologies to patient care.

Several speakers explored this challenge at the School of Medicine's Big Data in Precision Health Conference, which ran May 23-24 at the Li Ka Shing Center for Learning and Knowledge. Speakers from academia, government and industry shared lessons on wrangling immense data sets to develop useable, actionable solutions in health care and new lines of research.

"We've translated fundamental discoveries into advances in therapeutics, and we'll continue to do that," said medical school Dean Lloyd Minor, MD. "But now we also have the unique opportunity to make discoveries not necessarily based on mechanistic analyses, but on deriving information from vast treasure troves of data that already exist .... That's really the power of big data."

Keynote speaker Eric Dishman, director of the National Institutes of Health's All of Us research program, explained the program's mission: to gather health data from more than 1 million people in the United States to improve and accelerate health research and care.

While describing the aims of the program, Dishman related the story of his diagnosis, at age 19, with a rare form of kidney cancer. Doctors who saw the diagnosis extrapolated information from the average population of people who had his disease, most of whom were ages 65 to 70. He was told he had nine months to live. "It was a wake-up call to me," said Dishman, who is now 50. "Everyone is doing the best they can with the data they have, but it doesn't mean that's the truth for any given individual."

Precision health for the masses

The morning session of May 23 focused on questions about the body's transition from health to disease. Susie Spielman, director of strategic initiatives for Stanford's Department of Radiology, is a program leader for Project Baseline, a collaboration between Stanford, Duke and Verily that aims to map human health in unprecedented detail. She led off the session, detailing the project's goal of analyzing 10,000 individuals' health data to answer a question that's key to nearly all precision health research efforts: How do you define "normal" for any given individual?

"As we move to population cohorts, the scale increases to millions of individuals, and as genome sequencing continues to roll out, tens of millions of genetic variants. Data at that scale becomes quite challenging," said Manuel Rivas, PhD, an assistant professor of biomedical data science, who spoke on population health. That challenge, he said, is what motivates him to think about statistical methods and computational tools capable of carrying out analyses on massive amounts of data, creating summaries that are useful in answering questions fundamental to biology.

In the afternoon, the focus shifted to a high-profile embodiment of precision health today: cancer immunotherapy. Crystal Mackall, MD, professor of medicine and of pediatrics at Stanford, is a leading researcher in engineering immune cells to fight cancer. In back-to-back talks, she and Adnan Jairdar, MD, a medical officer at the Food and Drug Administration, detailed the yin and yang of innovation and regulation: how cutting-edge treatments that reprogram a patient's own immune cells to fight tumors make it out of the lab and into the hands of doctors.

Topping off the discussion on cancer immunotherapies, Jennifer Wargo, MD, associate professor of surgical oncology and of genomic medicine at MD Anderson Cancer Center, highlighted what she believes is an emerging frontier in precision health: the microbiome, or the microorganisms in our bodies. Her work looks at the connection between the makeup of the gut microbiome and immunotherapy success. Indeed, the type and number of bacteria living in a person's gut actually does alter the outcome of immunotherapies — a result that theoretically could enhance success of these kinds of cancer treatments, Wargo said.

'Man plus machine'

Day Two of the conference opened with a focus on machine learning and artificial intelligence, highlighting its purpose and potential in health care. Dekel Gelbman, the CEO of FDNA, a digital health platform that harnesses artificial intelligence to identify rare diseases based on physical facial features, said that the role of the company's facial recognition capabilities is to augment diagnoses. Clinicians using the technology report accurate diagnoses, and that's great, he said. But the best feedback is when they say the platform helped show them diagnostic information they wouldn't have otherwise seen.

Andrew Ng, PhD, an adjunct professor of computer science at Stanford and a globally recognized leader in artificial intelligence, brought the power of AI in diagnostics to the stage in a demonstration of a smartphone app that processes pictures of X-ray images and spits out the likely medical conditions associated with the X-ray's composition.

"Because AI technology is still evolving … only AI experts have a very good sense of the potential of AI, while only health care experts have a very good sense of how health care could benefit," Ng said. "The approach that I believe will be successful in this era is getting AI people to learn more about health care, and get health care people to learn more about AI."

The final conference session focused on digital health. Four speakers discussed the intersection of health, digital technologies, venture capitalism, quality of life and behavior as it relates to health.

"We often hear about the fear that robots are going to take over and kill us all," said Rich Mahoney, PhD, CEO of Seismic, which creates wearable robotics. Mahoney's technology is called Powered Clothing and looks like a pliable combination of undergarments and a bodysuit. But integrated into the fabric are electromechanical muscles that work to boost the wearer's core muscles. With sensors that can feel the motion of the person, Powered Clothing is designed to tell when a person is, for example, standing up, and physically helps to bring them upright. The technology could help improve the quality of life for older individuals who may be experiencing a loss of mobility.

"We don't specify other industries as 'digital.' It's not 'digital transportation' or 'digital manufacturing,'" said Lisa Suennen, senior managing director at GE Ventures, who said she views technology as a means to better patient care. "We need to get to a point where we're comfortable enough with technology in health care that it's simply part of health care." ISM

Data

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Mello said she was somewhat surprised by the survey results, "given the amount of consternation one hears at conferences about data sharing."

"Interestingly, nearly half our sample had experienced a breach of their personal data privacy in another context, yet they were still willing to share their clinical trial data," she said.

Then again, she said, people who take part in clinical trials may be special.

"I suspect that clinical trial participants may be different from the public at large," Mello said. "They are already incurring risks to benefit science by dint of their trial participation."

Most of those participants, along with clinical researchers, believe the benefits of sharing data include accelerating scientific discovery and improving accurate reporting of trial results.

Companies leery of data sharing

Yet some investigators and industry sponsors of clinical trials are leery of the swift move toward broad data sharing because of "potential harm to research participants," the authors wrote. "Investigators express worries that participants' privacy cannot be adequately protected, particularly in light of the fact that experts have demonstrated that it is possible to reidentify participant-level data."

Furthermore, the authors wrote, some pharmaceutical companies have warned that data sharing could chill people's willingness to participate in trials, thereby delaying the availability of new therapies. In fact, 31 percent of those surveyed were somewhat or very concerned about having their personal information stolen. Nevertheless, most felt the benefits of data sharing were more important.

"Reaching a world in which the sharing of clinical trial data is routine requires surmounting several challenges — financial, technical and operational," the authors wrote. "But in this survey, participants' objections to data sharing did not appear to be a sizeable barrier."

Former Stanford researcher Van Lieou also co-authored the study.

The study was funded by the Greenwall Foundation and the National Institutes of Health.

Stanford's departments of Health Research and Policy and of Medicine and the Stanford Law School also supported the work. ISM

Millions could have incorrect prescriptions, study asserts

By Beth Duff-Brown

More than 11 million Americans may have incorrect prescriptions for aspirin, statins and blood pressure medications, according to a study led by researchers at the School of Medicine.

Their findings are based on an updated set of calculations — known as pooled cohort equations, or PCEs — that are used to determine the risk of a heart attack or stroke.

The PCEs are the foundation for cardiovascular-disease-prevention guidelines in the United States. They help physicians decide whether to prescribe aspirin, blood pressure or statin medications, or some combination of these, by estimating the risk a patient may have for a heart attack or stroke. Most physicians calculate a patient's risk using a PCE web calculator or a smartphone app; the equations are also built into many electronic health records so that a patient's risk is automatically calculated during an office visit.

But there has been debate over whether the PCEs are based on outdated data and therefore putting some patients at risk for over- or under-medication.

"We found that there are probably at least two major ways to improve the 2013 equations," said Sanjay Basu, MD, PhD, assistant professor of primary care outcomes research at the School of Medicine and a core faculty member at Stanford Health Policy. "The first was well-known: that the data used to derive the equations could be updated."

Old equations

For example, he said, one of the main data sets used to derive the original equations had information from people who were 30-62 years old in 1948, and who would therefore be 100 to 132 years old in 2018 — that is, likely dead. The older equations were often estimating people's risk as too high, possibly by an average of 20 percent across risk groups.

"A lot has changed in terms of diets, environments and medical treatment since the 1940s," Basu said. "So, relying on our grandparents' data to make our treatment choices is probably not the best idea."

Basu is the senior author of the study, which was published June 5 in the *Annals of Internal Medicine*. The lead author is Steve Yadlowsky, a graduate student in electrical engineering at Stanford.

Furthermore, the researchers found that the old data may not have had a sufficient sample of African-Americans. For many African-Americans, physicians may have been estimating the risks of heart attacks or strokes as too low.

"So while many Americans were being recommended aggressive treatments that they may not have needed according to current guidelines, some Americans — particularly African-Americans — may have been given false reassurance and probably need to start treatment given our findings," Basu said.

The researchers have updated the PCEs with newer data in an effort to substantially improve the accuracy of the cardiovascular risk estimates. The National Institutes of Health, which maintains and updates the cohort data, approved the updated equations.

Updating statistical methods

A second improvement to the equations, the authors found, was to update the statistical methods used to derive the equations.

"We found that by revising the PCEs with new data and statistical methods, we could substantially improve the accuracy of cardiovascular disease risk estimates," the authors wrote.

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.

Basu is a member of Stanford Bio-X and the Child Health Research Institute

Researchers from the University of Michigan, University of Washington and University of Mississippi also contributed to the study.

The study was supported by the National Institutes of Health and a Stanford University graduate fellowship.

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

Neurons

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hospital leaves a blood sample, and often these samples are frozen and stored for future study. This technique is a breakthrough that opens the possibility to learn about complex disease processes by studying large numbers of patients."

A paper describing the findings were published online June 4 in the *Proceedings of the National Academy of Sciences.* Wernig is the senior author. Former postdoctoral scholar Koji Tanabe, PhD, and graduate student Cheen Ang are the lead authors.

Dogged by challenges

The transdifferentiation technique was first developed in Wernig's laboratory in 2010 when he and his colleagues showed that they could convert mouse skin cells into mouse neurons without first inducing the cells to become pluripotent — a developmentally flexible stage from which the cells can become nearly any type of tissue. They went on to show the technique could also be used on human skin and liver cells.

But each approach has been dogged by challenges, particularly for researchers wishing to study genetically complex mental disorders, such as autism or schizophrenia, for which many hundreds of individual, patient-specific samples are needed in order to suss out the relative contributions of dozens or more disease-associated mutations.

"Generating induced pluripotent stem cells from large numbers of patients is expensive and laborious. Moreover, obtaining skin cells involves an invasive and painful procedure," Wernig said. "The prospect of generating iPS cells from hundreds of patients is daunting and would require automation of the complex reprogramming process."

Although it's possible to directly convert skin cells to neurons, the biopsied skin cells first have to be grown in the laboratory for a period of time until their numbers increase — a process likely to introduce genetic mutations not found in the person from whom the cells were obtained.

The researchers wondered if there was an easier, more efficient way to generate patient-specific neurons.

'Somewhat mindboggling'

In the new study, Wernig and his colleague focused on highly specialized immune cells called T cells that circulate in the blood. T cells protect us from disease by recognizing and killing infected or cancerous cells. In contrast, neurons are long and skinny cells capable of conducting electrical impulses along their length and passing them from cell to cell. But despite the cells' vastly different shapes, locations and biological missions, the researchers found it unexpectedly easy to complete their quest.

"It's kind of shocking how simple it is to convert T cells into functional neurons in just a few days," Wernig said. "T cells are very specialized immune cells with a simple round shape, so the rapid transformation is somewhat mind-boggling."

The resulting human neurons aren't perfect. They lack the ability to form mature synapses, or connections, with one another. But they are able to carry out the main fundamental functions of neurons, and Wernig and his colleague are hopeful they will be able to further optimize the technique in the future. In the meantime, they've started to collect blood samples from children with autism.

"We now have a way to directly study the neuronal function of, in principle, hundreds of people with schizophrenia and autism," Wernig said. "For decades we've had very few clues about the origins of these disorders or how to treat them. Now we can start to answer so many questions."

Other Stanford co-authors are postdoctoral scholars Soham Chanda, PhD, and Daniel Haag, PhD; undergraduate student Victor Olmos; professor of psychiatry and behavioral sciences Douglas Levinson, MD; and professor of molecular and cellular physiology Thomas Südhof, MD.

The research was supported by the National Institutes of Health, the California Institute for Regenerative Medicine, the New York Stem Cell Foundation, the Howard Hughes Medical Institute, the Siebel Foundation and the Stanford Schizophrenia Genetics Research Fund.

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

Test

continued from page 1

due date, but ultrasound gives less reliable information as a pregnancy progresses, making it less useful for women who don't get early prenatal care. Ultrasound also requires expensive equipment and trained technicians, which are unavailable in much of the developing world. By contrast, the researchers anticipate that the new blood test will be simple and cheap enough to use in low-resource settings.

'Super-high-resolution view of pregnancy'

The gestational-age test was developed by studying a cohort of 31 Danish women who gave blood weekly throughout their pregnancies. The women all had full-term pregnancies. The scientists used blood samples from 21 of them to build a statistical model, which identified nine cell-free RNAs produced by the placenta that predict gestational age, and validated the model using samples from the remaining 10 women. The estimates of gestational age given by the model were accurate about 45 percent of the time, which is comparable to 48 percent accuracy for first-trimester ultrasound estimates.

Measuring cell-free RNA in mothers' blood also could provide a wealth of new information about fetal growth, Ngo said. "This gives a super-high resolution view of pregnancy and human development that no one's ever seen before," she said. "It tells us a lot about human development in normal pregnancy."

To figure out how to predict preterm birth, the researchers used blood samples from 38 American women who were at risk for premature delivery because they had already had early contractions or had given birth to a preterm baby before. These women each gave one blood sample during the second or third trimester of their pregnancies. Of this group, 13 delivered prematurely and the remaining 25 delivered at term. The scientists found that levels of cell-free RNA from seven genes from the mother and the placenta could predict which pregnancies would end early.

"It's mostly maternal genes," Moufarrej said, noting that the genes that predict prematurity are different than those that give information about gestational age. "We think it's mom sending a signal that she's ready to pull the ripcord."

Biology of preterm birth still mysterious

The scientists need to validate the new tests in larger cohorts of pregnant women before they can be made available for widespread use. A blood test to detect Down syndrome that was developed by Quake's team in 2008 is now used in more than 3 million pregnant women per year, he noted.

The biological mechanism behind preterm birth is still a mystery, but the scientists plan to investigate the roles of the genes that signal prematurity to better understand why it happens. They also hope to identify targets for drugs that could delay premature birth.

Other Stanford authors of the paper are graduate student Keli Liu; postdoctoral scholar Joan Camunas-Soler, PhD; research affiliates Wenying Pan, PhD, Jennifer Okamoto and Norma Neff, PhD; senior research scientist Ronald Wong; Robert Tibshirani, PhD, professor of biomedical data science and of statistics; Gary Shaw, DrPH, professor of pediatrics; and David Stevenson, MD, professor of pediatrics.

Scientists from the Statens Serum Institute in Copenhagen, the University of Pennsylvania School of Medicine and the University of Alabama-Birmingham also contributed to the study.

Quake, Tibshirani, Shaw and Stevenson are members of Stanford Bio-X; Tibshirani, Shaw and Stevenson are members of the Stanford Child Health Research Institute; Quake and Tibshirani are members of the Stanford Cancer Institute; Stevenson is an affiliate of the Stanford Woods Institute for the Environment; and Quake is a member of the Stanford Cardiovascular Institute, Stanford ChEM-H and the Stanford Neurosciences Institute.

The research was funded by the Bill and Melinda Gates Foundation, the March of Dimes Prematurity Research Center at Stanford University, the March of Dimes Prematurity Initiative Grant at the University of Pennsylvania and the Chan Zuckerberg Biohub, of which Quake is co-president.

The Chan Zuckerberg Biohub has submitted a patent application for the new technology.

Stanford's departments of Bioengineering, Applied Physics and Pediatrics also supported the work. The Department of Bioengineering is jointly operated by the schools of Medicine and of Engineering. ISM

5 QUESTIONS

an occasional feature in which an expert answers five questions on a science or policy topic

Stephen Luby discusses the deadly Nipah virus

A little-known virus discovered 20 years ago could become the next global pandemic.

A recent outbreak of Nipah virus in South India has renewed interest in the disease, which can spread from fruit bats or pigs to humans. It kills nearly three-quarters of the people who become infected. There is no vaccine for it and no cure, and it has many strains capable of spreading from person to person, increasing the chances of a strain emerging with the ability to rapidly spread among South Asia's densely populated communities and beyond.

Stanford scientists have illustrated potential pathways between people and bat secretions, shown Nipah contaminating hospital surfaces and piloted a way of preventing transmission. Stephen Luby, MD, professor of infectious diseases, has co-authored recent studies linking changes in temperature with the virus' spread from bats to humans and examining the impact of behavioral changes that reduce the likelihood of people consuming potentially virus-contaminated tree sap.

Luby is also a senior fellow at the Stanford Woods Institute and the Freeman Spogli Institute for International Studies and a member of Stanford Bio-X and the Stanford Child Health Research Institute. He spoke with writer Rob Jordan about risks posed by the current Nipah virus outbreak and interventions that could slow or halt its transmission.

1 How might Nipah adapt to more efficient human-to-human transmission and thereby become a global pandemic threat?

LUBY: It is conceivable that there is currently a strain of Nipah virus circulating among bats that, if it infected people, would efficiently transmit from person to person. So far, we have not identified such a strain.

Characteristics that might increase the risk of person-to-person transmission would be a virus that has a stronger tendency to move to the respiratory tract in high numbers. It is conceivable that the virus could acquire a mutation that would enhance this capacity. One concern is that anytime a virus infects a human, it is in an environment that selects for survival in that context.

2 What role, if any, does land conversion have in altering the epidemiology of infectious diseases, including the emergence of novel infections such as Nipah?

LUBY: The natural habitat for Nipah-carrying Pteropus bats is tropical forests. As these forests have been converted into agricultural lands, the bats have sought out other sources of food. In Bangladesh, the virus moves from bats to people because the bats are licking fresh date palm sap and so passing their saliva — which occasionally is infected with Nipah virus — on to people who drink the sap. Because of habitat loss, Pteropus bats in Australia are more likely to stay in suburbs where fruit trees are available, and people and horses are nearby. The bats have halted much of their annual migration because of habitat loss.

Stephen Luby

3 Why are emerging diseases such as Nipah important to study?

LUBY: Emerging infections have resulted in the most devastating infectious diseases that humanity has ever faced. These include HIV, tuberculosis, measles and smallpox. History has taught us that emerging infections can be major threats.

4 How can the global community thoughtfully respond to the threat?

LUBY: Both Ebola outbreaks and hospital-based transmission of Nipah illustrate that hospitals in low-income countries are important sites for transmission of potential pandemic organisms. We cannot predict which organism is likely to be the next pandemic, nor are we likely to have everyone vaccinated against these unknown threats. There has been much less enthusiasm for efforts to reduce the risk of transmission in low-income-country hospitals. This requires addressing difficult problems with adequate supplies, behavior and accountability. In addition to developing vaccines and drugs, improving conditions in health care facilities is a key step for reducing global risk. As an example, [postdoctoral scholar] Lily Horng of Stanford has published nice work on the difficulty of implementing basic hand-hygiene practices in Bangladesh hospitals.

Investing in research to develop and test new strategies for sustaining improved infection-control practices in low-income-country hospitals would be a particularly useful area for research. It would also be useful to enhance surveillance, so we have a better idea about where the human cases are occurring, how many there are, what strains are involved and what pathway the virus is using to infect people.

5 Nipah was discovered 20 years ago, and there is still no vaccine. Why?

LUBY: Vaccine development requires large amounts of money. The number of people infected with Nipah is small, and so, until very recently, there has been limited investment in developing a vaccine. The Coalition for Epidemic Preparedness Innovations recently announced plans to fund the development of a human vaccine against Nipah. **ISM**

Dry

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to ward off dry mouth, but its side effects, including nausea and potential low blood pressure, are common, so it is rarely used in the clinic, Le said.

Many of the saliva-producing cells that are needed to keep the mouth constantly moist are found in a pair of structures called the submandibular glands, tucked under the lower jawbone on each side of the chin. Radiation often kills these cells and, more troublingly, also salivary stem and progenitor cells, those juvenile members of the population that are needed to rebuild and restore the capacity to make saliva.

Daria Mochly-Rosen

Quynh-Thu Le

The key to retaining salivary function is protecting these rare but critical stem and progenitor cells. That's tricky because, following radiation therapy, toxic, highly reactive compounds called aldehydes are created in the gland, gumming up cellular function.

Le, the Katharine Dexter McCormick and Stanley McCormick Memorial Professor, who specializes in treating head and neck cancer, said she had spent a decade hearing from her patients about their struggles with dry mouth. "I wanted to do something," she said.

Her initial strategy was to try to regenerate salivary stem cells and, while working with these cells, her lab found that they contain high levels of an enzyme called aldehyde dehydrogenase 3A1, or ALDH3A1. The enzyme is a member of the large aldehyde dehydrogenase family of enzymes, proteins that initiate or speed up chemical reactions, that can defang troublesome aldehydes. But ALDH3A1 isn't a match for the radiation-unleashed aldehydes on its own.

She needed to find something to amp it up.

Looking to the East

Le had met with Mochly-Rosen through SPARK, a program founded and co-directed by Mochly-Rosen, that shepherds basic science discoveries into the clinic. Mochly-Rosen, who is the George D. Smith Professor in Translational Medicine, had been working on aldehyde dehydrogenases for more than a decade and had obtained access to a library of 135 traditional Chinese medicine extracts.

Many of those extracts have been used as treatments for various ailments in humans for hundreds of years, boosting the likelihood they are safe to use, Mochly-Rosen said.

Her team found that seven of these 135 extracts boosted ALDH3A1 activity. It was up to Saiki to see if she could break apart these complex natural extracts — from plants including tangerine, lotus and an Asian rhizome known as zhi mu in Chinese — to find out what, exactly, was activating the enzyme.

"She did the unthinkable, a really amazing achievement. She found the single active ingredient that activates the enzyme, ALDH3A1," Mochly-Rosen said.

Admittedly, Mochly-Rosen and Saiki said, a bit of luck and a fair amount of trial-and-error were involved. D-limonene stood out from other compounds in the extracts because it is broken down relatively quickly in the body and has been deemed by the Food and Drug Administration as a food flavor "generally recognized as safe" and has been approved for use as a food additive, Saiki said.

Saiki said she was pleasantly surprised by her finding. "It's a very common molecule, and sometimes as a scientist you wonder, Why hasn't anyone seen this before?" she said.

Next, they had to see if d-limonene would rev up ALDH3A1 in living cells.

Testing in mice, and humans

A series of experiments with mouse cells that had been exposed to radiation showed that d-limonene reduced aldehyde concentrations in both adult and salivary stem and progenitor cells. Even when the cells were treated weeks after radiation exposure, d-limonene still improved their ability to recover, repair gland structure and produce saliva. Mice that ate d-limonene and were exposed to radiation also produced more saliva than mice that did not receive d-limonene and were exposed to radiation. The researchers also learned that d-limonene wasn't likely to boost saliva production so high that mice, or humans, would be drooling — the compound didn't increase saliva production in mice that hadn't been exposed to radiation. And they confirmed that d-limonene did not affect tumor growth or interfere with the tumor-shrinking effects of the radiation in mice.

> "She found the single active ingredient that activates the enzyme."

A further set of experiments pulled back the curtain on d-limonene's work: It was stopping the expression of messages that trigger the salivary stem and progenitor cells to self-destruct.

Buoyed by these positive results, the researchers wanted to know if the compound had any hope of helping patients. To work, it would have to be active inside the salivary glands. To find out, they launched a phase-0 study, an early clinical trial in a small number of patients to see if d-limonene, taken by mouth in a capsule, would be distributed to the salivary gland. Four participants who were having a salivary gland tumor removed took d-limonene for two weeks before the surgery. When the tissue was examined after it was removed, researchers found high levels of d-limonene, showing that it has the potential to be used therapeutically in humans — it reaches the salivary gland tissue.

The patients did experience one quirky side effect: citrus-infused burps.

Next, the team plans to start the clinical trial process, which will take several years and require a multi-institutional collaboration, Le said. "If it works, then this type of drug would be used safely to prevent dry mouth in patients in the long run and make it much easier for patients to tolerate the radiation treatment with an improved quality of life after the treatment," she said.

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.

The study's other Stanford authors are life science research assistant Hongbin Cao; postdoctoral scholars Lauren Van Wassenhove, PhD, Vignesh Viswanathan, PhD, Dhanya Nambiar, PhD, and Matthew Stevens, PhD; life science researcher Joshua Bloomstein; former postdoctoral scholar Dadi Jiang, PhD; senior research scientist Che-Hong Chen, PhD; clinical research coordinator Amanda Simmons; graduate student Hyun Park; biostatistician Rie von Eyben; Eric Kool, PhD, professor of chemistry; and Davud Sirjani, MD, clinical assistant professor of otolaryngology-head and neck surgery.

Researchers from the University of California-San Francisco also contributed to the study.

The research was funded by grants from the National Institutes of Health.

Stanford's departments of Chemical and Systems Biology and of Radiation Oncology also supported the work. **ISM**

Grant awarded to study whether stem cells can treat urinary incontinence

School of Medicine researcher Bertha Chen, MD, has been awarded $5.98 million by the California Institute for Regenerative Medicine to investigate ways of using a person's own stem cells to treat urinary incontinence.

The award was one of four given out May 24 by the state stem cell agency as part of its Translation Research Program, which aims to help move promising stem cell research out of the laboratory and into the clinic.

Bertha Chen

Urinary incontinence affects about 30 percent of adult women ages 30 to 60 and is one of the most common indications for surgery in elderly women. However, as many as one-third of the women either cannot undergo surgery or will not benefit from surgery. The condition can have a significant impact on quality of life and be emotionally devastating.

Chen, professor of obstetrics and gynecology, and her team are exploring ways to use stem cells to generate the smooth muscle cells in the urinary tract that are lost in a person with urinary incontinence. If the approach works, it could also lead to new ways to treat other urinary or digestive problems caused by a loss of smooth muscle.

Other translational grants announced at the meeting included $1.7 million to Max BioPharma Inc. to pursue a stem-cell-based treatment for osteoporosis; $4.77 million to researchers at the University of California-Irvine to investigate how to regenerate damaged retinas; and $1.7 million to researchers at Children's Hospital Oakland Research Institute to develop a prenatal test for some types of blood cell disorders that could be amenable to early stem-cell-based treatments.

The institute also awarded nearly $12 million to researchers at UCLA to test a therapy for advanced nonsmall cell lung cancer that combines a well-known immunotherapy called pembrolizumab with an approach that genetically modifies immune cells called dendritic cells to enhance their ability to activate cancer-fighting T cells. **ISM**

Howard Chang named Howard Hughes Medical Institute investigator

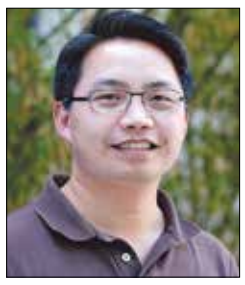
Howard Chang, MD, PhD, professor of dermatology and of genetics at the School of Medicine, is among 19 scientists from 15 institutions announced as new Howard Hughes Medical Institute investigators.

HHMI provides each investigator with a full salary, benefits and a research budget over the initial seven-year appointment, which may be renewed for additional terms. The institute also covers other expenses, including research space and the purchase of critical equipment.

Stanford's other new HHMI investigator is Elizabeth Sattely, PhD, assistant professor of chemical engineering. With today's appointments, the university now has 24 HHMI investigators.

"Every scientist is unique, but they all need one thing: time," said HHMI President Erin O'Shea in announcing the new recipients. "HHMI is dedicated to providing outstanding biomedical scientists with the time and resources to do their best work. We think of this as investing in people, not just projects."

Chang's research focuses on understanding how small molecules attached to the DNA affect gene expression and coordinate cell fate and function, as well as on the role played by long noncoding RNAs and other RNA structures in biological regulation.



Howard Chang

Noncoding RNAs do not code for proteins and until relatively recently had been considered to be biologically inconsequential. But research by Chang and others has shown that these molecules, particularly long noncoding RNAs, or lncRNAs, are critical to many processes, including those involved in normal development and cancer.

"I am delighted and honored to receive the HHMI appointment," Chang said. "HHMI's long-term support will allow my team to pursue high-risk and high-reward projects that may take a long time to pay off. The flexible funding of HHMI will also allow us to pursue new technologies and ideas as they emerge about how to control genes to enhance human health."

Chang is the director of the Center for Personal Dynamic Regulomes at Stanford and the Virginia and D.K. Ludwig Professor of Cancer Genomics. He is a core investigator at the Parker Institute for Cancer Immunotherapy at Stanford. He is also a member of Stanford's Child Health Research Institute, Cancer Institute, Neurosciences Institute, ChEM-H and Bio-X. **ISM**

OF NOTE

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

MARK BUYYOUNOUSKI, MD, was promoted to professor of radiation oncology, effective May 1. He specializes in genitourinary cancers, with a research focus on prostate cancer. He also leads multi-institutional clinical trials.

JEREMY DAHL, PhD, was promoted to associate professor of radiology, effective May 1. His research focuses on devising and implementing ultrasonic methods that are capable of generating high-quality images in difficult-to-image patients, and on developing new ultrasonic imaging devices.

TUSHAR DESAI, MD, was promoted to associate professor of medicine, effective May 1. He specializes in the treatment of general pulmonary and interstitial lung diseases. His research focuses on lung stem cells, lung cancer and pulmonary fibrosis, using a combination of genetic mouse models and human tissue.

HEATHER DESJARDINS-PARK, a third-year medical student, received the 2018 Peter J. Gingrass, MD Memorial Award from the Plastic Surgery Research Council for the best paper by a medical student or nonplastic surgical resident. Her winning paper, "Beyond antibiotics: Local doxycycline administration reduces scarring and improves wound healing by modulating scarring fibroblast behavior," appeared in *Plastic and Reconstructive Surgery.*

KIM HAZARD, MD, was promoted to associate professor of pathology and of pediatrics, effective May 1. Her research interests include characterizing pediatric tumor pathology, evaluating abnormalities of the juvenile reproductive system and demonstrating changes brought by metabolic disorders to cell structure and tissue of specific organs.

GORDON LEE, MD, professor of plastic and reconstructive surgery, received the 2018 Annual Presidential Award from the California Society of Plastic Surgeons in recognition of exemplary service.

DANIEL PALANKER, PhD, professor of ophthalmology and director of Stanford's Hansen Experimental Physics Laboratory, and **KULDEV SINGH**, MD, professor of ophthalmology, were in the top 20 of *The Ophthalmologist*'s Power List 2018. The British magazine's list features 100 of the world's most influential physicians, vision scientists and business leaders selected from international nominations.

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, was awarded the 2018 A.E. Bennett Award from the Society of Biological Psychiatry. This award recognizes superb international research in biological psychiatry and includes $5,000. He was honored for developing self-organizing, realistic human brain organoids to gain insights into psychiatric disorders. He was also among five medical "visionaries" named by *The New York Times* in a May 24 article that discussed their work.

BRENDA PORTER, MD, PhD, was promoted to professor of neurology and neurological sciences, effective April 1. She specializes in difficult-to-treat epilepsy, particularly in children with neuronal-developmental disorders. Her clinical research focuses on improving outcomes in epilepsy surgery and in the prevention of epilepsy in patients with tuberous sclerosis.

JAGANNATH PADMANABHAN, PhD, postdoctoral scholar in plastic and reconstructive surgery, received a $10,000 Combined Pilot Research Grant from The Plastic Surgery Foundation. The award aims to accelerate the translation of scientific discoveries and technical developments into practical solutions. He is investigating the cell types and molecular pathways that drive biomedical implant rejection.

DANIELLE ROCHLIN, MD, resident in plastic and reconstructive surgery, received the J.K. Hardesty, MD, Best Resident Paper Award from the California Society of Plastic Surgeons. Her paper, "Postoperative pathway associated with shorter length of stay after free autologous breast reconstruction," was presented at the society's annual meeting.

GEORGE SLEDGE, MD, professor of medicine and chief of oncology, was selected as the 2018 inductee in breast cancer in the Giants of Cancer Care program organized by OncLive, a group of specialized publications. The program celebrates physicians who have made significant contributions to cure and treat cancer.

MICHAL TAL, PhD, a postdoctoral scholar in immunology and in stem cell biology and regenerative medicine, received a 2018 Emerging Leader Award from the Bay Area Lyme Foundation. The $100,000 award is designed to encourage promising scientists who are the future of Lyme disease-research leadership. She will study how the bacterium that causes Lyme disease uses the protein CD47 to evade the immune system. **ISM**

Mark Buyyounouski

Jeremy Dahl

Tushar Desai

Heather desJardins-Park

Kim Hazard

Gordon Lee

Daniel Palanker

Kuldev Singh

Sergiu Pasca

Brenda Porter

Jagannath Padmanabhan

Danielle Rochlin

George Sledge

Michal Tal