INSIDE STANFORD MEDICINE

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Two researchers urge greater regulatory oversight of e-cigarettes in developing countries.

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Researchers engineer yeast to produce opioid compounds

ROD SEARCEY

Christina Smolke led the decade-long effort to genetically engineer yeast so that it is able to convert sugar into opioid compounds.

By Tom Abate

For thousands of years, people have used yeast to ferment wine, brew beer and leaven bread.

Now Stanford researchers have genetically engineered yeast to make painkilling medicines, a breakthrough that heralds a faster and potentially less expensive way to produce many different types of plant-based medicines.

Writing Aug. 13 in *Science*, the engineers describe how they reprogrammed the genetic machinery of baker's yeast so that these fast-growing cells could convert sugar into hydrocodone in just three to five days.

Hydrocodone and its chemical relatives, such as morphine and oxycodone, are opioids, members of a family of painkilling drugs sourced from the opium poppy. It can take more than a year to produce a batch of medicine, starting from the farms in Australia, Europe and elsewhere that are licensed to grow opium poppies. Plant material must then be harvested, processed and shipped to pharmaceutical factories in the United States, where the active drug molecules are extracted and refined into medicines.

"When we started work a decade ago, many experts thought it would be impossible to engineer yeast to replace the entire farm-to-factory process," said senior author Christina Smolke, PhD, associate professor of bioengineering.

Now, though the output is small — it would take 4,400 gallons of bioengineered yeast to produce a single dose of pain relief — the experiment proves that bioengineered yeast can make complex, plant-based medicines.

"This is only the beginning," Smolke said. "The techniques we developed and demonstrate for opioid pain relievers can be See OPIOIDS, page 6

Bacterial community in pregnant women linked to preterm birth

By Erin Digitale

Risk for premature birth is linked to the composition of the vaginal bacterial community in the mother during pregnancy, according to a study from the School of Medicine that tracked women's microbial communities on a week-by-week basis during pregnancy.

A high-diversity pattern of vaginal bacterial raised the likelihood of premature birth, and the longer the bacteria followed this pattern, the higher the risk, the study found. The study may also help explain why prematurity risk is elevated in women who have closely spaced pregnancies.

A paper describing the research was published online Aug. 17 in the *Proceedings of the National Academy of Science*s.

Babies born more than three weeks early are considered premature. About 450,000 premature infants are born each year in the United States. Prematurity is the leading cause of newborn deaths. About half of such births occur after spontaneous preterm labor, whose triggers are not well-understood.

"We wanted to develop a baseline understanding of what happens to the human microbiome during pregnancy, both in women who deliver healthy, term babies and in those who deliver prematurely," said the study's senior author, David See PREMATURITY, page 7

PRAESING / SHUTTERSTOCK

A specific pattern of high diversity in the vaginal bacteria of pregnant women raises the likelihood of premature birth, according to a new study.

Unique genes in Khoe-San people may lower risk of some pregnancy hazards

By Jennie Dusheck

An examination of the immune genes of the southern African Khoe-San people has revealed a completely new kind of mutation, according to researchers at the School of Medicine. The gene variant likely contributes to healthier babies, although the variant can also lower resistance to disease.

The findings grew out of a long-term effort by Peter Parham, PhD, professor of structural biology and of microbiology and immunology, to understand how immune system genes make us reject organ transplants.

A paper detailing the findings was published online Aug. 20 in *PLOS Genetics.* The gene variant was one of two they found that would be expected to alter the formation of the placenta during early pregnancy, leading to larger, healthier babies and a reduced risk of pre-eclampsia, a major cause of maternal death.

"Only a handful of studies have investigated the function of immune genes in African populations. As a result, we have probably greatly underestimated the breadth of human immune variation," said Parham, the study's senior author. "So we were excited to investigate the Khoe-San, a divergent, modern human popula- See KHOE-SAN, page 7

Brain scans better forecast math learning in kids than skill tests do

By Erin Digitale

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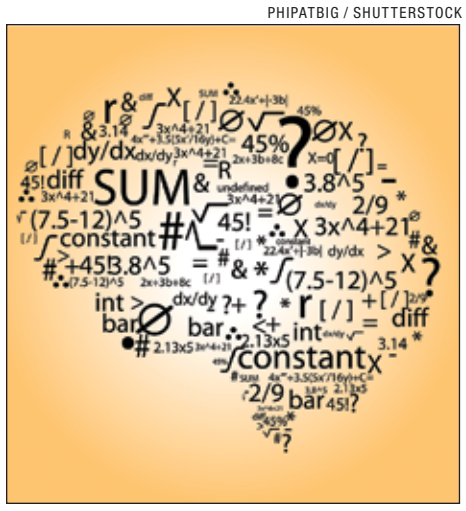

Brain scans from 8-year-old children can predict gains in their mathematical ability over the next six years, according to a new study from the School of Medicine.

The research tracked 43 children longitudinally for six years, starting at age 8, and showed that while brain characteristics strongly indicated which children would be the best math learners over the following six years, the children's performance on math, reading, IQ and memory tests at age 8 did not.

The study, which was published online Aug. 18 in *The* See MATH, page 6

Test identifes gene defects in heart patients more accurately

By Jennie Dusheck

For the subset of heart patients whose illness isn't caused by a lifetime of cigarettes, trans fats or high glycemic foods, a new genetic test developed at the School of Medicine may be able to accurately pinpoint the likely genetic causes of their conditions in just a couple of days.

In work that could advance precision health, Kitchener Wilson, MD, PhD, instructor of pathology, and Joseph Wu, MD, PhD, professor of cardiovascular medicine and of radiology, teamed up with a group of genome-sequencing specialists to develop the new technique: a better way to test cardiac patients for any genes that might be causing their problems.

Wilson and Wu said that the gold standard of genome sequencing involves thousands of genes, costs $1,000 or more and can take weeks or months to get results. For a patient with a heart condition that's difficult to diagnose, it makes no sense to sequence the entire 22,000-gene genome, since fewer than 200 genes are known to affect the heart, they said. Moreover, whole-genome sequencing typically contains mistakes, so key mutations might be missed.

To meet this challenge, Wilson and Wu's team designed a streamlined assay, or test, that looks at just the 88 genes known to carry mutations that cause heart problems. Materials for the new test cost about $100, and results are back within three days. Wilson and Wu are first and senior authors, respectively, on a paper describing the assay that was published online Aug. 11 in *Circulation Research*.

This approach — surveying a small subgroup of relevant genes instead of the whole genome — is already used to test for other diseases, such as cystic fibrosis. But cystic fibrosis involves only one gene, albeit with hundreds of variants. "By comparison, the heart diseases are more challenging just because there are so many genes to sequence," said Wilson. "To do that accurately has been difficult and, until now, too expensive for most labs."

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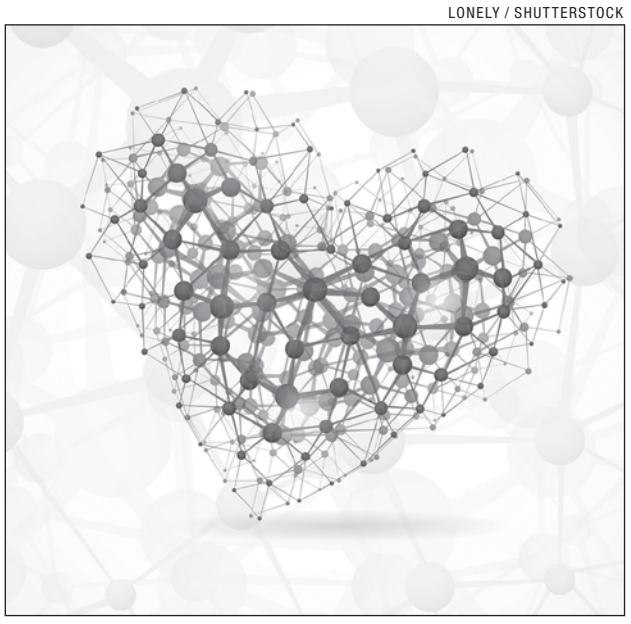

Kitchener Wilson

Joesph Wu

Simple genetic probes

Such testing isn't for the typical, older cardiac patient who comes in with chest pain, the result of a lifetime of poor diet and little exercise. "Those patients can be treated with standard treatments, such as surgical interventions. But what if a 30-year-old woman comes in with chest pain and her doctors can't find any obvious reason why she should be having heart problems at such a young age?" said Wu, who is also the director of Stanford's Cardiovascular Institute. That could be the moment for doctors to break out the complementary long padlock probes for inherited heart disease.

Complementary long padlock probes, or cLPPs, were developed at the Stanford Genome Technology Center by senior research scientist Curt Scharfe, MD, PhD, research scientist Peidong Shen, PhD, and their colleagues. These simple probes accurately target specific parts of the genome and can be made in large batches at low cost. Because of their simplicity, they are easily customized to target different genes. Wilson and Wu spearheaded the effort to put cLPPs to work diagnosing cardiac diseases. "The work was very much a collaboration between clinicians and technologists," said Wilson. (Scharfe and Shen are co-authors of the paper.)

> "Our goal is to make genetic testing more accessible to more people."

A preliminary test of the assay on blood samples and some skin samples from 29 participants from families with inherited heart disease validated the cLPP approach, the researchers said. The heart disease cLPP assay was cheaper, faster and more accurate than whole-genome assays.

The Stanford team next plans to test the technique on a group of 200-300 patients. In the meantime, Wilson and Wu are offering the test free to any research lab that wants to try it. "They can just email me," said Wilson, "and we'll send them the assay, and then they can do it in their own lab — as long as they have some experience with next-generation sequencing."

The assay will shorten the time it takes to diagnose difficult or unusual heart disease cases, Wu said. "Suppose you have a 60-year-old patient who comes in with heart failure," he said. "We do the angiogram and we find he has no history of heart attack or other issues, and yet the heart is not performing well. We also find that several of his family members have similar heart conditions. So if we run the new genetic test and find the man's illness has a genetic cause, such as dilated cardiomyopathy, we now have both a cause and a diagnosis, and we can initiate treatment right away."

Avoiding a 'fishing expedition'

"Not having that result delays diagnosis and increases costs because you're going through a whole bunch of tests — sometimes it becomes a fishing expedition, which can be frustrating to both the physician and the patient," Wu added. "But perhaps the most important benefit is that you can give the patient accurate answers about his or her disease."

Wilson and Wu said the genome technology group has been working on the cLPP technique for a long time. "Our goal is to make genetic testing more accessible to more people," Wilson said. "We want to democratize it. For now, we're going to release it free of charge: Researchers can get samples of the assay so they can run it themselves. We're also releasing all of the technical data for the probes so researchers can recreate and modify the probes themselves. In some ways it's making genetic testing open source."

The development of the new test is an example of Stanford Medicine's focus on precision health, which aims to enable researchers and physicians to better predict individual risks for specific diseases, develop approaches to early detection and prevention, and help clinicians make real-time decisions about the best way to care for patients.

Other Stanford-affiliated authors of the paper are Eula Fung, MS, clinical data analyst; Ioannis Karakikes, PhD, instructor in cardiovascular medicine; Stanford undergraduate Angela Zhang; Kolsoum InanlooRahatloo, PhD, postdoctoral scholar; Justin Odegaard, MD, PhD, instructor of pathology; Karim Sallam, MD, cardiovascular medical fellow; Ronald Davis, PhD, professor of biochemistry and of genetics; George Lui, MD, professor of cardiovascular medicine and of pediatrics; and Euan Ashley, MD, PhD, professor of cardiovascular medicine.

This work was supported by the National Institutes of Health, the Stanford Cardiovascular Institute, the Steven M. Gootter Foundation and the American Heart Association.

Stanford's departments of Pathology, Medicine and Radiology also supported the work. ISM

Finding usable medical images made easier through software

By Kim Smuga-Otto

Medical education instructors often rely on images to communicate what they're teaching, whether it's the latest innovations in heart-valve replacement or the practicalities of surgery during humanitarian missions.

And though images can be found online pretty easily, determining the legality of using them is often considerably more challenging.

"If we have a two-hour online course, my guess is we spend 15 hours trying to figure out the copyright status of the presentations," said Linda Baer, director of continuing medical education at Stanford.

Now she — and anyone else looking for medical images — has a new resource to make that process easier: Bio-Image Search, developed by Lane Medical Library, serves up images and diagrams exclusively from medical and scientific organizations. It groups the results based on the degree to which their republication is allowed.

A search for "breast cancer" returned 135 images with no restrictions beyond citing their source, as well as another 104 images with some restrictions, all clearly indicated.

Baer is delighted by the site's ease of use and clear copyright information.

She said that it will make her and course designers' jobs easier.

While the search engine has access to over 2 million images, it has its limitations. It draws from only eight databases, and the majority of images come from PubMed Central. While PubMed articles are available for education purposes, the images within them might have different copyright restrictions that require contacting the publishers.

However, Tony Christopher, Lane's technology and customer support director who oversees the tool's development, feels the search will improve as more people use it. "Word is starting to spread," he said. Usage of the tool was up 60 percent in April compared to the previous months.

Bio-Image Search was originally called Lane Image Search when it launched in January. Its creator, web developer Alain Boussard, continues to upgrade the software and will be adding three more databases by the end of July.

It's not restricted to instructors; students writing papers, staff assembling presentations, or anyone visiting the website can access the tool. And as awareness grows, Christopher hopes Stanford researchers and departments will volunteer new image databases to integrate into the system.

But for Baer, even the current version is an improvement. "Having a resource where you can send someone makes everyone's lives simpler," she said.

To contribute images to Bio-Image Search, contact Tony Christopher at tonychristopher@stanford.edu or 721-5993.

More information about using Bio-Image Search is available at http://lane.stanford.edu/bioimagesearch.html ISM

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Stanford MEDICINE

5 QUESTIONS

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

Charlotte Jacobs on her side career as a writer

Early in her academic career, Charlotte Jacobs, MD, professor emerita of medicine at Stanford, focused her research and writing on solid cancerous tumors. When she later became associate dean, she wrote about medical education and clinical training. Simmering below these endeavors, however, was a desire to also pursue a different kind of writing.

Her first biography, Henry Kaplan and the Story of Hodgkin's Disease, *was published in 2010. Her most recent book,* Jonas Salk: A Life, *was published in the spring. It tells the story of the brilliant and complicated physician who discovered and developed the first vaccine for polio. In a recent interview, Jacobs, the Drs. Ben and A. Jess Shenson Professor in the School of Medicine, Emerita, talked with writer Penny Hodgson about her dual careers in medicine and writing.*

1 What originally led you to a side career as a biographer?

JACOBS: I loved biography from childhood. Years later, during a sabbatical year at Stanford, I decided to take creative writing. I was interested mainly in biography writing, but I knew I had to develop the craft and the skills of a writer first.

Then two things converged: Henry Kaplan, the eminent Stanford radiation oncologist and cancer pioneer, died very quickly of lung cancer. He was an amazing man who designed the first linear accelerator and with Saul Rosenberg was responsible in large part for the cure for Hodgkin's disease. At the same time that Kaplan died, my creative-writing instructor introduced me to Ehud Havazelet, a fellow at Stanford who went on to teach creative writing at Oregon State and the University of Oregon.

We started a weekly writing seminar. My homework was working on my biography of Henry Kaplan. I was doing research on his life and work, conducting interviews, and also studying the craft of biography writing. I went from being hooked on reading biography as a child to being hooked on writing biography as an adult.

2 How are you able to meld your doctor life with your writer life?

JACOBS: Oncology is a positive field. There are not too many subspecialties in medicine, except infectious disease, in which you cure someone. There aren't many opportunities to follow someone for 10 years after you've treated them for an advanced, life-threatening disease. In oncology, I see cancer patients get married, have children and go on to live a normal life. This is incredibly rewarding.

That said, I don't meld my oncology life with my biographer life at all. When I'm writing or doing research on one of my books, I'm totally focused on that. And when I'm with my patients, I'm totally focused on them. One thing I learned from Henry Kaplan, who had a whirlwind of activity surrounding him, was that when he was in the exam room, the patient was his only concern.

I do think my background in science helped me be a better writer, though. I chose subjects who were in the field of science or medicine because that is what I know. One of the hardest tasks was interpreting my subjects' work to the general public. I used to think if my next-door neighbor, who was a smart housewife, couldn't understand and enjoy the books, I had failed.

Knowing academic medicine also helped. Jonas Salk ran into major political hurdles, and he was not treated kindly — some of which was his own doing. Having spent my entire career in academic medicine, I could understand the world in which he worked.

MAX AGUILERA-HELLWEG

Charlotte Jacobs

3 Do you have a set schedule for writing?

JACOBS: I try to block off a half-day or two half-days a week to write. I applied for writing fellowships where for a month I did nothing but write. Every evening, other artists, writers and musicians talked about their work or had open studios or played their compositions. Those fellowships provided wonderful, creative time.

Whenever on vacation, whether skiing or at the beach, I took along my writing material. Or I'd try to squeeze in an hour at night after the kids were in bed. When my boys were playing upper-level soccer, we attended tournaments all around northern California. During the breaks between games, I sat in the car and wrote since they certainly didn't want to be around their mother.

I could find snippets during every day to write. Even today I find that to be the case.

4 How did you find publishers for your books?

JACOBS: Finding an agent is very hard, particularly for a first-time author. My husband got me the book *Publishing for Dummies*. I followed all the instructions, and I compiled a long list of agents. I had my A list, my B list and C list.

I sent out my first five queries to my dream agents, and to my surprise Robert Lescher asked me to come to New York and not to sign with anybody else. Although he was a well-known agent, he had trouble getting the Kaplan book published by any of the major houses, I think for a few reasons: One, I was an unknown author; two, my subject matter was not well-known to the general public; and three, as my first effort, I had not yet mastered the art of biography. So he started looking at academic presses, and I ended up at Stanford University Press.

My agent unfortunately died before the Salk book was finished, and I was at a loss because he had been an independent agent. So I contacted my friend Abraham Verghese [an author and Stanford professor of medicine], who recommended me to his agent, Mary Evans. Through Mary, I was introduced to a highly talented young agent, Rachel Vogel. She had a bidding war going on over my Salk biography within a short period of time.

It came down to my choosing between a popular press, which wanted the book to be much shorter and cover just some aspects of Salk's life, and Oxford University Press, which wanted a traditional, first, formal biography of Jonas Salk. It was an easy choice.

5 Beside the two biographies, you have also performed in community theater and written something else. Can we end by your telling me a little about this other work?

JACOBS: I co-wrote a musical comedy with a composer-lyricist who's won a number of Emmys. It's called *Just My TYPE* and is based on the Myers-Briggs Type Indicator. It has gone through a number of readings in the Bay Area with subsequent rewrites. Now we have an agent in New York who is showing it around to different new-works programs.

I've enjoyed collaborating on a musical comedy almost as much as working on the biographies. Yet my greatest fulfillment still comes from caring for patients with cancer. **ISM**

Standardized agreements to expedite trial contracts

Stanford University has joined more than 200 academic institutions and hospitals in adopting standardized research and confidentiality agreements for use in industry-sponsored clinical trials.

The agreements have been preapproved by participating institutions and organizations, and when used will expedite the process of starting a study.

Clinical research studies are essential to translate knowledge gained in the laboratory into interventions that improve human health. Multisite studies are critical because many diseases require large numbers of participants to yield valid findings. However, launching human studies at multiple institutions is complicated and can sometimes take months. There are many contributors to these delays, but a prime cause is the review and negotiation process for various agreements at each participating institution.

Data from a study that examined contracts processing for 2010 Clinical and Translational Science Awards revealed that an average contract negotiation time of 55 days, exclusive of budget and safety-board approvals, could be reduced to 22 days if a master agreement was used.

> "Using these agreements will make it significantly faster for Stanford investigators to launch new clinical studies."

"Using these agreements will make it significantly faster for Stanford investigators to launch new clinical studies and easier for them to collaborate with peer institutions and industry," said Harry Greenberg, MD, the medical school's senior associate dean for research and the director of Spectrum, the Stanford Center for Clinical and Translational Research and Education.

Stanford representatives were part of the working group that developed the agreements over the last two-and-a-half years. The group also included representatives from the Clinical and Translational Science Awards consortium, industry and the University Industry Demonstration Partnership. The initiative was funded by the National Center for Advancing Translational Sciences within the National Institutes of Health.

To date, about 50 organizations representing more than 225 research sites have agreed to the terms of the agreements and accept them without revisions. Stanford's Research Management Group is now using the clinical trial and confidentiality agreements when appropriate, and they plan on adopting a new agreement designed for use with outsourced contract research organizations after it is finalized by the working group in the next few weeks.

For more information, visit www.ara4us.org. **ISM**

Spectrum accepting grant proposals for team projects tackling health-care problems

Spectrum, the Stanford Center for Clinical and Translational Research and Education, is accepting funding applications for teams of multidisciplinary investigators tackling health-care problems through novel approaches.

Grants of up to $50,000 will be awarded in five areas: medical technologies; therapeutics; population health; community engagement; and predictive tools and diagnostics.

In addition, grants of up to $50,000 will be awarded through the Stanford Learning Health Care Innovation Challenge, which funds projects to improve the health of patient populations served by Stanford Health Care.

Last year, Spectrum awarded about $1.1 million to 32 projects.

For more information and to submit applications, which are due Sept. 30, visit http://spectrum.stanford.edu/accordions/innovations-pilots. **ISM**

E-cigarettes could have health impacts in developing world

By Ruthann Richter

Most of the debate around e-cigarettes has focused on the developed world, but the devices are becoming more widely available in some low- and middle-income countries, where there is even greater potential for impact on public health, according to two School of Medicine researchers.

"People don't think e-cigarettes will reach the developing world. But they are already being produced in developing countries, and they are cheap. People know they are available," said Andrew Chang, MD, a resident in internal medicine who focuses on global health.

Chang and Michele Barry, MD, director of the Stanford Center for Innovation in Global Health, are co-authors of a commentary on e-cigarettes that was published in the Aug. 18 issue of the *Journal of the American Medical Association.*

According to the World Health Organization, global use of e-cigarettes is booming, with more than half of the world's population living in countries where the devices are available. Global sales of e-cigarettes reached $3 billion in 2013 and are expected to grow to $10 billion by 2017, the WHO projects.

Public awareness of the devices is high in some developing countries. In the recent International Tobacco Control survey, 34 percent of adults in Mexico, 35 percent in Brazil and 62 percent in Malaysia said they had heard about the devices or tried them. In some of the poorest regions of the world — notably Africa and South Asia — there is little known about e-cigarette use, though these are vast potential markets, the authors wrote.

"They are cheap. People know they are available."

Supporters of e-cigarettes tout the devices as a smoking-cessation tool and a safe alternative to smoking traditional cigarettes, yet there is a lack of research to support these arguments, the authors noted. In fact, data suggests that in the process of aerosolizing nicotine, e-cigarettes may produce known carcinogens, such as formaldehyde and acetone. And though the devices may have lower nicotine levels, they still carry the potential for addiction, with potentially harmful effects on the body, particularly the cardiovascular system, the authors wrote.

Luring young smokers

Chang said a major concern is that marketers of e-cigarettes may use them in poorer countries as a mechanism to recruit new smokers, particularly young smokers, offering the devices at low cost and then raising prices later, forcing users to switch to conventional cigarette products.

"What we are most concerned about is the entry of big tobacco on a global scale in which they could hijack the harm-reduction potential and recruit new and never users into smoking," he said.

Nicotine exposure is a major contributor to cardiovascular disease, which remains one of the leading causes of death in the developing world, where access to primary care interventions, such tools to control blood pressure and lower cholesterol, are often scarce, Chang said. Exposure to e-cigarettes also may exacerbate lung problems, such as tuberculosis or lower respiratory tract infections, which are highly prevalent in the developing world, he said.

Because of the potential for harm, Chang and Barry urge developing countries to exert greater regulatory control over e-cigarettes, also known as electronic nicotine delivery systems. ENDS are banned in some countries, including Brazil, Uruguay and Singapore, but in some regions, regulatory control has been hampered by difficulty in determining whether e-cigarettes should be classified as consumer goods, controlled substances or medical devices, they noted.

"Developing nations should not underestimate the availability and targeted marketing of ENDS within their borders and should place e-cigarettes under the purview of their medical and pharmaceutical regulatory boards," they wrote.

The authors also urge nongovernmental organizations, such as the Gates Foundation and the Bloomberg Initiative to Reduce Tobacco Use, to support regulatory control and enforcement of the devices.

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

MARC BRUXELLE / SHUTTERSTOCK

According to the World Health Organization, global use of e-cigarettes is booming, with more than half of the world's population living in countries where the devices are available.

Scientists observe atomic-resolution details of brain signaling

By Glenn Roberts Jr.

Scientists have revealed never-before-seen details of how the human brain sends rapid-fire messages between its cells.

Researchers at the School of Medicine and the Department of Energy's SLAC National Accelerator Laboratory mapped the 3-D atomic structure of a two-part protein complex that controls the release of signaling chemicals, called neurotransmitters, from brain cells. Understanding how cells release those signals in less than one-thousandth of a second could help launch a new wave of research on drugs for treating brain disorders.

The experiments, at the Linac Coherent Light Source X-ray laser at SLAC, build upon decades of previous research at Stanford and the national lab. A paper describing the findings was published online Aug. 17 in *Nature*.

"This is a very important, exciting advance that may open up possibilities for targeting new drugs to control neurotransmitter release," said Axel Brunger, PhD, professor and chair of molecular and cellular physiology and professor of neurology and neurological sciences. "Many mental disorders, including depression, schizophrenia and anxiety, affect neurotransmitter systems." Brunger, who is also professor of photon science at SLAC and a Howard Hughes Medical Institute investigator, is the senior author of the paper. The first author is postdoctoral scholar Qiangjun Zhou, PhD.

Unraveling the combined secrets of two proteins

"Both parts of this protein complex are essential," Brunger added, "but until now it was unclear how its two pieces fit and work together."

The two protein structures are known as neuronal SNAREs and synaptotagmin-1.

Earlier X-ray studies, including experiments at SLAC's Stanford Synchrotron Radiation Lightsource, or SSRL, nearly two decades ago, shed light on the structure of the SNARE complex, a helical protein bundle found in yeasts and mammals. SNAREs play a key role in the brain's chemical signaling by joining, or "fusing," little packets of neurotransmitters to the outer edges of neurons, where they are released and then dock with chemical receptors in another neuron to trigger a response.

In this latest research, the scientists found that when the SNAREs and synaptotagmin-1 join up, they act as an amplifier for a slight increase in calcium concentration, triggering a gunshot-like release of neurotransmitters from one neuron to another. They also found that the proteins join together before they arrive at a neuron's membrane, which helps to explain how they trigger brain signaling so rapidly.

"The neuron is not building the 'gun' as it sits there on the membrane — it's already there," Brunger said.

The team speculates that several of the joined protein complexes may group together and simultaneously interact with the same vesicle to efficiently trigger neurotransmitter release, an exciting area for further studies.

"The structure of the SNARE-synaptotagmin-1 complex is a milestone that the field has awaited for a long time, and it sets the framework for a better understanding of the system," said James Rothman, a professor at Yale University who discovered the SNARE proteins and shared the 2013 Nobel Prize in Physiology or Medicine.

Thomas Südhof, MD, a Stanford professor of molecular and cellular physiology and HHMI investigator who shared that 2013 Nobel Prize with Rothman, discovered synaptotagmin-1 and showed that it plays an important role as a calcium sensor and calcium-dependent trigger for neurotransmitter release.

"The new structure has identified unanticipated interfaces between synaptotagmin-1 and the neuronal SNARE complex that change how we think about their interaction by revealing, in atomic detail, exactly where they bind together," said Südhof, a co-author of the paper. "This is a new concept that goes much beyond previous general models of how synaptotagmin-1 functions."

Using crystals, robotics and X-rays to advance neuroscience

To study the joined protein structure, researchers in Brunger's laboratory at the School of Medicine found a way to grow crystals of the complex. They used a robotic system developed at SSRL to study the crystals at the Linac Coherent Light Source, an X-ray laser that is one of the brightest sources of X-rays on the planet.

The researchers combined and analyzed hundreds of X-ray images from about 150 protein crystals to reveal the atomic-scale details of the joined structure.

"This experiment was the first to use this robotic platform at LCLS to determine a previously unsolved structure of a large, challeng-

See PROTEIN, page 5

SLAC NATIONAL ACCELERATOR LABORATORY

From left, Axel Brunger, Artem Lyubimov, Qiangjun Zhou and Minglei Zhao view images from an experiment conducted at SLAC.

Mutations that contribute to rare blood cancer discovered

By Kim Smuga-Otto

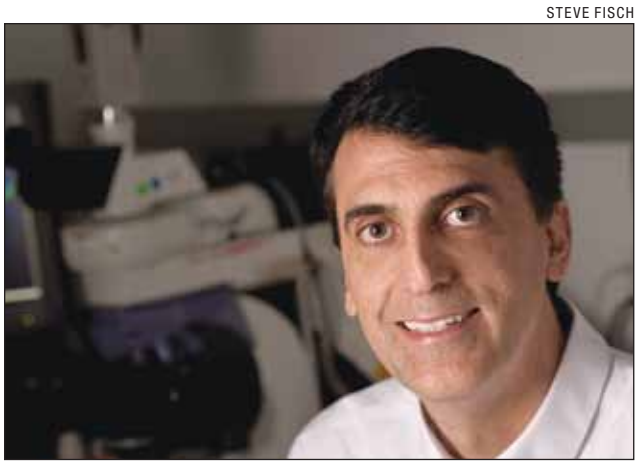
Researchers at the School of Medicine have identified a group of mutations responsible for many cases of a rare immune cell cancer called cutaneous T-cell lymphoma. Identifying the mutations could tip off clinicians to effective treatments for the currently incurable condition.

The mutations are found in 15 genes for proteins that work together in a T-cell-survival mechanism. When mutations prevent the mechanism from switching off, the T cells don't die when they should and actually keep multiplying.

The findings were published online Aug. 10 in *Nature Genetics*.

Cutaneous T-cell lymphoma — which manifests as rashes, skin tumors and leukemia — doesn't respond well to traditional chemotherapy, although a technique known as total skin electron radiation that was developed at Stanford can keep the skin disease at bay. Additionally, a new stem cell transplant therapy, also from Stanford, shows promise for long-term remission for those patients with advanced, high-risk disease.

STEVE FISCH



Paul Khavari is the senior author of a study identifying mutations that can cause an immune cell cancer called cutaneous T-cell lymphoma.

The newly identified cancer role of the proteins involved in the cell-survival mechanism suggests new strategies for fighting the disease: Researchers can look for drugs to counter the malfunctioning proteins resulting from the mutations.

"We can now design drug trials in a smart, evidence-based way that is specific to the patient," said Youn Kim, MD, professor of dermatology and one of the paper's authors.

But before doctors can prescribe drugs targeted to specific proteins, they'll need to know which, if any, mutations in the cell-survival pathway their patients' malignant T cells carry. In 60 percent of these cancers sequenced by the researchers, such mutations were absent.

"It really highlights that the future of many types of cancer treatment is going to be: first, know the cancer by sequencing it, and then tailor the therapy specifically," said senior author Paul Khavari, MD, PhD, professor and chair of dermatology.

Lead authorship is shared by graduate student Aparna Bhaduri, postdoctoral scholar Eon Rios, MD, PhD, and former postdoctoral scholar Alexander Ungewickell, PhD.

Only about 3,000 patients are diagnosed with cutaneous T-cell lymphoma each year in the United States. The most common form of the disease, mycosis fungoides, resembles common skin rashes — itchy, scaly, red skin eruptions that can cover the whole body. Although it manifests in the skin, the actual cancer cells are roaming immune cells called T cells that are programmed to defend the body from invaders in healthy individuals. In mycosis fungoides, these T cells remain in the skin and multiply excessively, resulting in rashes. In another stage, called Sézary syndrome, the abnormal T cells circulate in the bloodstream, spreading the cancer throughout the body.

Locked into always-on state

Khavari, the Carl J. Herzog Professor in Dermatology in the School of Medicine, likens skin T cells to patrolling sentries, rotating on and off duty. At the end of their shift, the cell-survival mechanism shuts down and, with no signal, the T cells leave or die. The mutations Khavari's team found prevent the pathway from turning off, causing T cells to pile up in the skin or circulate through the bloodstream. "More and more sentries keep showing up for duty," he said. "It's out of control."

Because of Kim's long commitment to treating mycosis fungoides and Sézary syndrome at Stanford, Khavari and his team were able to recruit 91 patients to sequence specific regions of the T cells' DNA they suspected might be modified in the cancer. From each patient, they collected both cancerous and healthy cells to compare their DNA. This way, they were able to discount any inherent mutations present in the patient before cancer. They identified 170 genes with mutations that could be related to the cancer.

In four of the patients examined, the researchers identified a mutation that replaced a specific amino acid in the tumor necrosis factor receptor 2, a protein embedded in the cell's membrane that receives signals from outside the cell. The mutation locked the receptor into an always-on state, preventing the cell-survival pathway from shutting down. Previous independent clinical studies found patients with increased TNFR2 protein in their bloodstream had more aggressive forms of the cancer that were more likely to return quickly after treatment. This led Khavari's team to look at the other patients' DNA to see if duplications could account for both the elevated levels in the blood and increased signaling to activate the cell-survival pathway. They found that 10 of the patients had multiple copies of the TNFR2 gene.

'Smoking gun'

The researchers confirmed the biological role of TNFR2 by growing cells in the lab with either the amino acid mutation or the duplicate TNFR2 genes and showing the cell-survival pathway to be more active than normal cells.

Although only 5 percent of the cancers had the TNFR2 mutation, the fact that it was the exact same mutation was a "smoking gun," according to Khavari, implicating the cell-survival mechanism's role in driving certain cutaneous T-cell lymphomas. While over half of the patients with the disease did not have these gene changes, identifying those who do presents new options for treating them.

Another one of the mutations caused a receptor that normally signals the cell-survival pathway to stop to instead activate it further and encourage cell proliferation. This receptor, CTLA4, has been identified in skin cancers, and an antibody that turns off the receptor has been approved as the drug ipilimumab to treat advanced melanoma. But before administering the drug, or less toxic alternatives, a physician would need to know if the patient had the mutated receptor; otherwise ipilimumab would have the opposite effect, deactivate a healthy protein and make the cancer worse.

University of California-San Francisco melanoma specialist Susana Ortiz-Urda, MD, PhD, who was not involved with the study, called the work groundbreaking and said she was impressed that the researchers were able to gather so many patients to identify the rare mutations. Ortiz-Urda, who co-directs the UCSF Melanoma Center, said she thought the next step was "putting the paper to work in a clinical setting" to see if patients with different mutations would respond to different drug treatments.

Kim, the Joanne and Peter Haas Jr. Professor in Cutaneous Lymphoma Research who directs Stanford's Multidisciplinary Cutaneous Lymphoma Program, plans to do just that, using the individual patients' cancer cell genetic sequences to design combinations of drugs that would hit multiple defective proteins to completely shut down the cell-survival mechanism.

Khavari's lab will be working to incorporate the mutations they identified into the DNA of living mice. This will allow them to study the mutated genes' effects, and the actions of new drugs on those genes, directly.

"Before we had this data, it was trial and error — we were totally blind," said Kim. "We're finally taking the blindfolds off."

Other Stanford-affiliated authors are postdoctoral scholars Carolyn Lee, MD, PhD, Ashley Zehnder, DVM, PhD, Jason Reuter, PhD, and Mahkam Tavallaee, PhD; research assistant Angela Mah; Michael Snyder, PhD, professor of genetics; Robert Ohgami, MD, PhD, clinical instructor of pathology; Dita Gratzinger, MD, PhD, assistant professor of pathology; and flow cytometrist Randall Armstrong.

This study was funded by the National Institutes of Health, the Office of Research and Development of the U.S. Department of Veterans Affairs, the Dermatology Foundation, the Haas Family Foundation, and the Drs. Martin and Dorothy Spatz Charitable Foundation.

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

Kim Smuga-Otto is a science-writing intern for the medical school's Office of Communication & Public Affairs.

Protein

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ing multi-protein complex," said Aina Cohen, PhD, co-head of the Structural Molecular Biology Division at SSRL, who oversaw the development of the highly automated platform used for the neuroscience experiment.

"This is a good example of how advanced tools, instruments and X-ray methods are providing us new insights into what are truly complex mechanisms," added Cohen, a co-author of the study.

Brunger said future studies will explore other protein interactions relevant to neurotransmitter release. "What we studied is only a subset," he said. "There are many other factors interacting with this system and we want to know what these look like. This by no means is the end of the story."

Other Stanford-affiliated authors of the study are postdoctoral scholars Ying Lai, PhD, Minglei Zhao, PhD, Monarin Uervirojnangkoorn, PhD, and Ucheor Choi, PhD; former postdoctoral scholars Taulant Bacaj, PhD, and Oliver Zeldin, DPhil; research specialists Artem Lyubimov, PhD, Jiajie Diao, PhD, and Richard Pfuetzner; and William Weis, PhD, professor of molecular and cellular physiology, professor and chair of structural biology and professor and chair of photon science at SLAC.

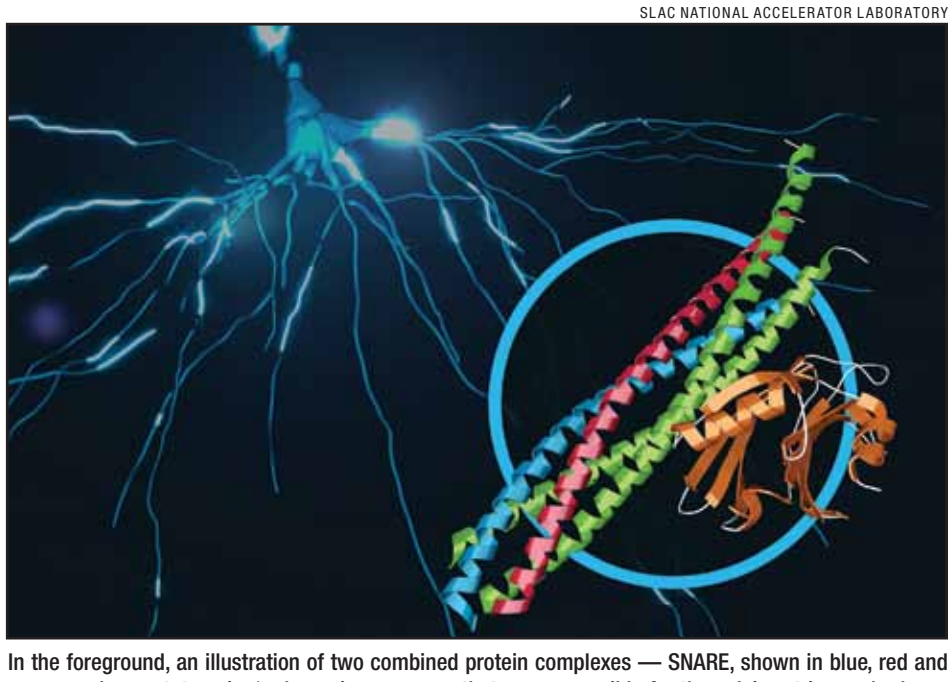
Other SLAC-affiliated authors are Michael Soltis, PhD, co-head of the Structural Molecular Biology Division at SSRL; associate scientist Roberto Alonso-Mori, PhD; staff scientist Matthieu Chollet, PhD; and former staff scientist Henrik Lemke, PhD.

Researchers at Lawrence Berkeley National Laboratory also contributed to the study.

The research was supported by HHMI, the National Institutes of Health, the DOE Office of Science and the SSRL Structural Molecular Biology Program, which is also supported by the DOE Office of Science and the NIH's National Institute of General Medical Sciences.

The study was also supported by X-ray experiments at SSRL and at Argonne National Laboratory's Advanced Photon Source, and by Stanford's departments of Molecular and Cellular Physiology and of Structural Biology. **ISM**

SLAC NATIONAL ACCELERATOR LABORATORY



In the foreground, an illustration of two combined protein complexes — SNARE, shown in blue, red and green, and synaptotagmin-1, shown in orange — that are responsible for the calcium-triggered release of neurotransmitters from our brain's nerve cells in a process called synaptic vesicle fusion. In the background, an illustration shows electrical signals traveling through a neuron.

Glenn Roberts Jr. is a science communications specialist at SLAC National Accelerator Laboratory.

Opioids

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adapted to produce many plant-derived compounds to fight cancers, infectious diseases and chronic conditions such as high blood pressure and arthritis."

From plant to test tubes

Many medicines are derived from plants, which our ancestors chewed or brewed into teas, or later refined into pills using chemical processes to extract and concentrate their active ingredients. Smolke's team is modernizing the process by inserting precisely engineered snippets of DNA into cells such as yeast to reprogram the cells into custom chemical assembly lines to produce medicinal compounds.

An important predecessor to the Stanford work has been the use of genetically engineered yeast to produce the antimalarial drug artemisinin. Traditionally, artemisinin has been sourced from the sweet wormwood tree in similar fashion to how opiates are refined from poppy. Over the last decade, as yeast-based artemisinin production has become possible, about one-third of the world's supply has shifted to bioreactors.

> "This is only the beginning."

The artemisinin experiments proved that yeast biosynthesis was possible, but involved adding only six genes. The Stanford team had to engineer 23 genes into yeast to create their cellular assembly line for hydrocodone.

"This is the most complicated chemical synthesis ever engineered in yeast," Smolke said.

Her team found and fine-tuned snippets of DNA from other plants, bacteria and even rats. These genes equipped the yeast to produce all the enzymes necessary for the cells to convert sugar into hydrocodone, a compound that deactivates pain receptors in the brain.

"Enzymes make and break molecules," said lead author Stephanie Galanie, a PhD student in chemistry and a member of Smolke's team. "They're the action heroes of biology."

To get the yeast assembly line going, the team had to fill in a missing link in the basic science of plant-based medicines.

Many plants, including opium poppies, produce (S)-reticuline, a molecule that is a precursor to active ingredients with medicinal properties. In the opium poppy, (S)-reticuline is naturally reconfigured into a variant called (R)-reticuline, a molecule that starts the plant down a path toward the production of molecules that can relieve pain.

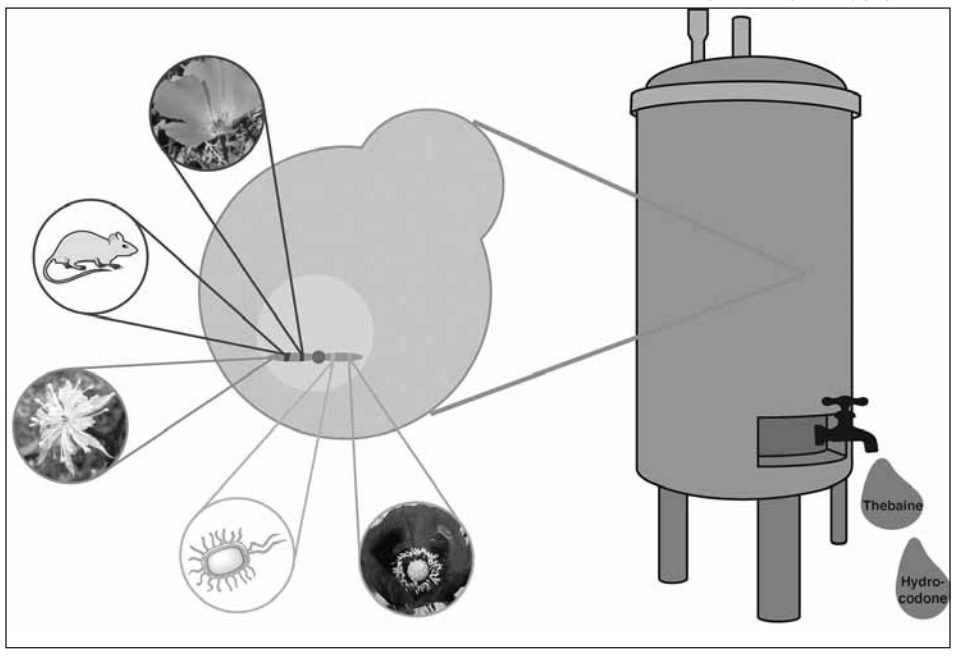
Smolke's team and two other labs recently independently discovered which enzyme reconfigures reticuline, but even after the Stanford bioengineers added this enzyme into their microbial factory, the yeast didn't create enough of the opioid compound. So they genetically tweaked the next enzyme in the process to boost production. Down the line they went, adding enzymes, including six from rats, in order to craft a molecule that emerged ready to plug pain receptors in the brain.

Engineered with a purpose

In their *Science* paper, the Stanford authors acknowledged that a new process to make opioid painkillers could increase concerns about the potential for opioid abuse.

"We want there to be an open, deliberative process to bring researchers and policymakers together," Smolke said. "We need options to help ensure that the bio-based production of medicinal compounds is developed in the most responsible way."

STEPHANIE GALANIE / SMOLKE LAB



The team succeeded in finding more than 20 genes from five different organisms — California poppy, rat, goldthread, bacteria and opium poppy — and engineering them into the genome of baker's yeast.

Smolke said that in the United States, where opioid medicines are already widely available, the focus is on potential misuse. But the World Health Organization estimates that 5.5 billion people have little or no access to pain medications.

"Biotech production could lower costs and, with proper controls against abuse, allow bioreactors to be located where they are needed," she said.

In addition to bioengineering yeast to convert sugar into hydrocodone, the Stanford team developed a second strain that can process sugar into thebaine, a precursor to other opioid compounds. Bio-produced thebaine would still need to be refined through sophisticated processes in pharmaceutical factories, but it would eliminate the time delay of growing poppies.

"The molecules we produced and the techniques we developed show that it is possible to make important medicines from scratch using only yeast," she said. "If responsibly developed, we can make and fairly provide medicines to all who need."

Stanford has patents on the technology, and Smolke and researchers on her team have formed a company. Other Stanford-affiliated co-authors of the paper are research associate Kate Thodey, PhD; postdoctoral scholar Isis Trenchard, PhD; and undergraduate Maria Filsinger Interrante.

The research was funded by the National Institutes of Health, the National Science Foundation, the ARCS Foundation and Stanford University.

Stanford's Department of Bioengineering also supported the work. The department is operated jointly by the School of Medicine and the School of Engineering. **ISM**

Math

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Journal of Neuroscience, moves scientists closer to their goal of helping children who struggle to acquire math skills.

"We can identify brain systems that support children's math skill development over six years in childhood and early adolescence," said the study's lead author, Tanya Evans, PhD, postdoctoral scholar in psychiatry and behavioral sciences.

STEVE FISCH

Vinod Menon is the senior author of a study that found that scans of children's brain structures indicated which childen would be the best math learners over the next six years.

"A long-term goal of this research is to identify children who might benefit most from targeted math intervention at an early age," said senior author Vinod Menon, PhD, professor of psychiatry and behavioral sciences. "Mathematical skills are crucial in our increasingly technological society, and our new data show which brain features forecast future growth in math abilities."

At the start of the study, the children received structural and functional magnetic resonance imaging brain scans. None of the kids had neurological or psychiatric disorders, and their intelligence fell in a range considered normal for their age. The scans were conducted while the children lay quietly in the scanner; the scans measured brain structure and intrinsic functional connections between brain regions, and were not tied to performance on any particular math task.

The 8-year-olds also took standardized tests (given outside the scanner) to measure IQ, as well as reading, math and working-memory skills. All of the children returned for at least one follow-up assessment of these skills before age 14, and many children had other additional follow-ups.

Surprising results

The scientists were surprised by the extent and nature of the connections between brain regions that predicted the development of the children's math skills. Greater volume and connectivity of two areas forecast skill development: the ventro-temporal occipital cortex, which is a brain region that supports visual object perception, and the intra-parietal sulcus, which helps people compare and make judgements about numbers, such as understanding that four is more than three. The strength of these regions' interconnections with the prefrontal cortex was also predictive. The work identifies a network of brain areas that provides a scaffold for long-term math skill development in children, Menon said.

The 8-year-olds' initial IQ, reading, working-memory and math scores did not predict long-term learning in math. The lack of predictive ability of standard math tests taken at age 8 suggests that brain features more precisely predict children's math learning, Evans said. The brain scans capture many different aspects of information processing, thus better forecasting which children will fall behind and which will excel, Menon added.

"Next, we are investigating how brain connections change over time in children who show large versus small improvements in math skills, and designing new interventions to help children improve their short-term learning and long-term skill acquisition," Menon said. Although it is still impractical to give brain scans to children on a large scale, the team's studies provide a baseline understanding of normal development that will help experts develop and validate remediation programs for children with learning disabilities, he noted.

In the meantime, the team's findings suggest that parents and teachers should encourage children to exercise their mental math muscles. "Just because a child is currently struggling doesn't necessarily mean he or she will be a poor learner in the future," Evans said.

Other Stanford co-authors were research assistants John Kochalka, Tricia Ngoon and Sarah Wu; instructor Shaozheng Qin, PhD; and postdoctoral scholar Christian Battista, PhD.

The research was funded by grants from the National Institutes of Health, the Stanford Child Health Research Institute, the Lucile Packard Foundation for Children's Health, Stanford's Clinical and Translational Science Award and the Netherlands Organization for Scientific Research. Menon is a member of the Stanford Child Health Research Institute.

Stanford's Department of Psychiatry and Behavioral Sciences also supported the research. **ISM**

Prematurity

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Relman, MD, professor of medicine and of microbiology and immunology at Stanford, and chief of infectious diseases at the Veterans Affairs Palo Alto Health Care System.

Missing puzzle piece

When the research began, little was known about whether or how the body's indigenous communities of bacteria change in pregnancy, said Relman, who is also a project leader at the March of Dimes Prematurity Research Center at Stanford. "It seemed like a big missing piece of the story."

Relman's team studied 49 pregnant women, 15 of whom delivered prematurely. The women gave weekly samples during pregnancy, and monthly samples for up to a year after delivery, that allowed researchers to characterize the bacterial communities in the vagina, lower gut, saliva and tooth and gum areas.

The scientists found that vaginal microbial communities fell into five patterns, consistent with prior research. For most women, the communities in the vagina and at the three other body sites did not change much during the course of pregnancy. "It's a bit surprising how stable the communities are, since there are lots of other body features that change dramatically in pregnancy, such as maternal hormone levels, metabolism and weight," said Relman, who holds the Thomas C. and Joan M. Merigan Professorship.

Four patterns of vaginal bacteria were characterized by little bacterial diversity and by dominance of various kinds of lactobacillus bacteria, which have been previously associated with health in women. None of these patterns were linked in the study to preterm birth.

The remaining pattern — characterized by greater bacterial diversity, high levels of gardnerella and ureaplasma bacteria, and low levels of lactobacillus — was linked with increased risk for preterm birth, especially if the bacterial community displayed this pattern for several weeks.

Daniel DiGiulio

David Relman

"I think our data suggest that if the microbiome plays a role in premature birth, it may be something that is long in the making," said the study's lead author, Daniel DiGiulio, MD, a research associate and clinical instructor in medicine. "It may be that an event in the first trimester or early second trimester, or even prior to pregnancy, starts the clock ticking."

Study co-author David Stevenson, MD, the principal investigator of the prematurity research center and director of the Johnson Center for Pregnancy and Newborn Services at Lucile Packard Children's Hospital Stanford, said the research "is part of our larger effort to find the microbial and immunological signature for preterm birth."

Big bacterial changes after birth

The researchers also found that, in all women, vaginal bacterial communities changed significantly after birth. This was true both of women who delivered prematurely and at term. The change was seen after both vaginal and cesarean deliveries. For up to a year after birth, women tended to have the more-diverse bacterial pattern. "This was a surprise," Relman said, adding that his team plans to conduct further research to find out whether the shift may help explain the increased risk for preterm birth in women whose pregnancies are closely spaced.

Though the findings need to be confirmed in a larger, more diverse group of women, they may ultimately help doctors identify which women are at risk for premature delivery, the researchers said. The findings also raise the possibility that treatment with probiotics or other interventions designed to alter the body's communities of bacteria may help ward off prematurity, a concept the researchers hope to test in future studies.

"Traditionally, we viewed microbes as pathogens — as bad actors," said DiGiulio. "We now recognize that our bodies' microbial communities perform many beneficial functions, yet there may be times when the communities get out of whack."

Other Stanford-affiliated co-authors of the study are research associates Benjamin Callahan, PhD, Elizabeth Costello, PhD, and Paul McMurdie, PhD; Deirdre Lyell, MD, associate professor of obstetrics and gynecology; Anna Robaczewska, MS, research assistant; postdoctoral scholars Christine Sun, PhD, and Daniela Goltsman, PhD; Ronald Wong, PhD, senior research scientist; Gary Shaw, DrPH, professor of pediatrics; and Susan Holmes, PhD, professor of statistics. Lyell, Shaw and Stevenson are members of Stanford's Child Health Research Institute.

The research was funded by the March of Dimes Prematurity Research Center at Stanford University, the National Institutes of Health, the Stanford Child Health Research Institute and the National Science Foundation. Stanford's Department of Medicine and Department of Microbiology and Immunology also supported this work. ISM

Khoe-San

continued from page 1

tion known to harbor enormous genetic diversity."

A genetic 'railway' switch

Mutations can alter genes in all kinds of ways. A mutation can have no effect on how a gene operates, it can change functionality in minor or important ways, or it can completely destroy normal function. Geneticists have never seen this type of mutation before, the researchers said. Originating among the Khoe-San, the mutation does two things at once: It simultaneously turns off one function and turns on another, much like a railway switch, pushing gene function off one track and onto another.

The Khoe-San — known for the unusual clicking sounds in their language — harbor unusually high genetic diversity, about 10 times more among their 100,000 people than among modern Europeans.

"The Khoe-San is one of the oldest populations of humans, so every population that's branched off from them has just a part of their genetic diversity. Every time the human population splits, there's slightly less diversity. So that's the reason the Khoe-San were so interesting to us," said co-author Paul Norman, PhD, a senior research scientist. One reason the Khoe-San are so diverse is that they are descended from an ancient population that was much larger.

Khoe-San genomes are an excellent place to look for unusual human genes. "We knew we'd find novel genes," said Hugo Hilton, DVM, a research scientist and lead author of the paper. "Our work has allowed us to understand the evolution of these genes, not only in the Khoe-San but in populations around the world."

The immune system genes of interest to Parham's team code for two sets of proteins. On the surfaces of ordinary cells are proteins called HLAs, which mark cells in ways so specific that a person's immune system recognize cells as self or not self. If a surgeon transplants a kidney, the recipient's immune system can tell that the kidney is someone else's — just from its cell surface HLA proteins — and the patient's immune system signals its natural killer cells, or NK cells, to attack the transplanted kidney.

The most varied genes

HLA genes are the most variable of the genome. So Parham and others have been trying to measure how much HLA genes vary within and between populations around the world. If you look at the population of the Bay Area, for example, you'll find hundreds of variants, because people come from all over the world. "In the Khoe-San, there are 10 or 11 variations of one of these genes, whereas when we looked at Amerindians a few years ago, they basically only had one version," said Norman. Doing organ transplants among people with few variants is relatively easy, whereas doing the same transplant among the Khoe-San would be difficult.

NICOLAS PERRAULT

The Khoe-San people of southern Africa — known for the unusual clicking sounds in their language — harbor unusually high genetic diversity.

To recognize HLA proteins, NK cells deploy receptor molecules called killer-cell immunoglobulin-like receptors, or KIRs, which bind to foreign HLA proteins. In most people in the world, one kind of KIR receptor binds to HLA C2 cell surface proteins, and another kind binds to HLA C1 proteins. The difference between the two kinds of proteins is critical. If you have an infection, you might want those NK cells to latch onto C2 molecules. If you are carrying a baby, however, you don't.

> "The Khoe-San is one of the oldest populations of humans."

That's because special NK cells in the uterus play an important role in reproduction by regulating the blood supply to a developing embryo. "The NK cells are involved at the beginning of pregnancy in helping develop the maternal blood vessels in the placenta, where they can supply a lot more blood to the developing embryo," said Parham.

The placenta is the interface between the embryo and the mother. Early in pregnancy, when the placenta is forming, the mother's NK cells bind to the embryo's placental cells. Sometimes, the mother doesn't have the gene for the C2 protein but the embryo does, having received the gene from its father. In that case, the mother's NK cells attack the C2-marked cells, leading to a poorly formed placenta that delivers insufficient blood to the fetus, a common problem that leads to low birthweight babies. The problem is also associated with dangerous high blood pressure, or pre-eclampsia, in the mother.

Binding more C1 and less C2 reduces these risks, and the novel version of the KIR gene that Parham's team found does just that. It no longer binds to C2 and instead has switched to binding C1. Immune cells are renowned for their ability to respond with great specificity to other molecules, so the researchers said it's remarkable that a small mutation could completely reverse the specificity of a receptor.

Parham's team also found a second variant of the KIR gene among the Khoe-San. This KIR allele simply makes a damaged receptor that does not bind to C2. Together, these two gene alleles greatly reduce the frequency of C2 receptors and increase C1 receptors in Khoe-San, presumably making for healthier babies.

Other Stanford-affiliated authors of the paper are research assistant Neda Nemat-Gorgani, MS; postdoctoral scholars Ana Goyos, PhD and Christopher Gignoux, PhD; and senior research scientist Lisbeth Guethlein, PhD. They collaborated with researchers at the University of California-San Francisco and Stony Brook University.

The work was supported by the National Institutes of Health, the March of Dimes Prematurity Research Center at Stanford University and the School of Medicine.

Stanford's departments of Structural Biology, Microbiology and Immunology, and Genetics also supported the work. ISM

Five faculty members appointed to endowed professorships


James Chang


Jeffrey Feinstein


Mary Hawn


Calvin Kuo


Ivan Soltesz

Four Stanford Medicine faculty members were recently appointed to endowed professorships.

JAMES CHANG, MD, professor and chief of plastic and reconstructive surgery, has been appointed the Johnson & Johnson Professor, effective June 11. His research focuses on tissue engineering, and his clinical specialty is reconstructive surgery of the hand.

This professorship was established at the School of Medicine in 1978 as one of six chairs provided to medical schools by Johnson & Johnson Corp. to support the activities of surgery departments in patient care, research and teaching. Ralph Greco, MD, professor and chief of surgery, currently holds the professorship but will be moving to emeritus status at the end of August.

JEFFREY FEINSTEIN, MD, MPH, professor of pediatrics, was appointed the Dunlevie Family Professor of Pulmonary Vascular Disease, effective June 11. He specializes in pediatric cardiology, pulmonary hypertension, pulmonary vascular disease, pulmonary vascular abnormalities and congenital heart defects. The professorship was established with an existing endowment fund, the Endowed Directorship of the Vera Moulton Wall Center. This professorship was converted from a directorship established in 2010 by Bruce and Elizabeth Dunlevie.

MARY HAWN, MD, professor and chair of surgery, was appointed the Stanford Medicine Professor of Surgery, effective June 11. She specializes in surgical quality and effectiveness.

This professorship was established with internal funds, as well as funds from Stanford Health Care and from Lucile Packard Children's Hospital Stanford, to honor former department chair Thomas Krummel, MD, the Emile Holman Professor in Surgery, the Susan B. Ford Surgeon-in-Chief at Lucile Packard Children's Hospital Stanford and co-director of Stanford Biodesign.

CALVIN KUO, MD, PhD, professor of medicine, was appointed the Maureen Lyles D'Ambrogio Professor II, effective June 11. His research focuses on developing methods to grow tissues and tumor samples to create therapies for cancer patients and discover cancer-related genes. He also studies stem cell biology in the gastrointestinal tract, and examines the role of blood vessels in diseases such as stroke, cancer and diabetes.

This professorship was established through the transfer of funds from the existing Maureen Lyles D'Ambrogio Professorship and additional funds from the Department of Medicine and the dean's office. The Maureen Lyles D'Ambrogio Professorship was established in 1970, with a gift of real estate from N.J. D'Ambrogio, '17, of Carmel, California, to honor his daughter, who died of cancer in 1967. The professorship was established to support research on cancer.

IVAN SOLTESZ, PhD, was appointed the James R. Doty Professor in Neurosurgery and Neurosciences, effective June 11. His research focuses on the function and dysfunction of neuronal networks, and the mechanisms of circuit dysfunction in epilepsy. He has developed experimental methods for the control of epilepsy.

The professorship was established with a gift from Doty, MD, professor of neurosurgery at Stanford and director of the Center for Compassion and Altruism Research and Education. **ISM**

OF NOTE

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

RAMIN DUBEY, PhD, a postdoctoral scholar, was awarded a young investigator grant by Alex's Lemonade Stand Foundation to study toxicity and resistance to chemotherapy drugs using a genetic tool called haploid genetic screening to uncover the genes that mediate resistance to the topoisomerase inhibitors that form the basis for several cancer treatments. Dubey will receive $100,000 in grant funding over two years.

NASIDE GOZDE DURMUS, PhD, a postdoctoral scholar in biochemistry, is featured in *MIT Technology Review's* annual "35 Innovators Under 35" list. She invented a cell-levitating device that enables researchers to quickly detect physical changes in cells. White and red blood cells, cancer cells and cells that are responding to drugs all levitate at different heights in a magnetic field. Durmus' invention exploits this property of cells and makes it easy to spot how a cell responds to a drug in just an hour. This invention can also distinguish circulating tumor cells from whole blood without using any labels or antibodies, unlike the conventional methods.

MICHAEL IV, MD, clinical assistant professor of radiology, has been awarded a research scholar grant by the Radiological Society of North America Research and Education Foundation. He will receive $150,000 over two years for research that uses images of superparamagnetic iron oxide nanoparticles to track tumor-associated macrophages in a form of human brain tumor called glioblastoma multiforme.

GUILLEM PRATX, PhD, associate professor of radiation oncology, was awarded one of six 2015 Damon Runyon-Rachleff Innovation Awards. He will receive $300,000 over two years to develop a new way to use flow cytometry, a technology used to categorize single cells, to measure the uptake of any nonfluorescent molecule. This work will help researchers assess how tumors respond to cancer therapy. The award is given to early career scientists whose research aims to improve the prevention, diagnosis and treatment of cancer.

HYONGSOK SOH, PhD, was appointed professor of radiology and of electrical engineering, effective July 1. Soh's laboratory develops synthetic reagents and biosensor devices that measure biomolecules, such as nucleic acids and proteins, in complex environments. Recently, his team demonstrated a biosensor technology that can continuously measure drugs in live subjects in real time.

JENNIFER TREMMEL, MD, assistant professor of medicine, was appointed the Susan P. and Riley P. Bechtel Medical Director, an endowed position that supports her existing role as the clinical director of the Women's Heart Health Program at Stanford Health Care. The focus of Tremmel's research is sex differences in cardiovascular disease. She researches how men and women differ in coronary endothelial function, plaque deposition and the circulation of blood in the smallest blood vessels in those who have chest pain despite having normal-appearing coronary arteries. Tremmel is the inaugural holder of the directorship.

OANA URSU and **KUN-HSING YU**, both PhD students, have been selected as Howard Hughes Medical Institute international student fellows. The program provides $43,000 to life-sciences students during their third to fifth years of graduate school in the United States. This year, HHMI selected 45 PhD students from 18 countries to receive fellowships.

MICHAEL ZEINEH, MD, PhD, assistant professor of radiology, has been granted a clinical scientist development award from the Doris Duke Charitable Foundation. The award provides $162,000 per year for three years. Zeineh will use it to study iron and microglia in postmortem brain specimens from humans with Alzheimer's disease, with the aim of translating his findings to help people living with the disease. **ISM**


Ramin Dubey


Naside Gozde Durmus


Michael Iv


Guillem Pratx


Hyongsok Soh


Jennifer Tremmel


Michael Zeineh

Alpha Omega Alpha at Stanford elects new members

Alpha Omega Alpha is a national medical honor society that supports initiatives to enhance education, teaching, research, professionalism, humanism and service. The Stanford association of the society, which has more than 600 members, recently elected the following new members:

LINDA BOXER, MD, PhD, professor of hematology and vice dean of the School of Medicine.

KATHARINE BROCK, MD, a former fellow in pediatric hematology/oncology.

EDWARD DAMROSE, MD, associate professor of otolaryngology-head and neck surgery.

KARL DEISSEROTH, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences, and the D.H. Chen Professor.

ANN CAROLINE FISHER, MD, clinical assistant professor of ophthalmology.

ADAM GOMEZ, MD, resident in anatomic and clinical pathology. **ISM**

Medical students awarded Albert Schweitzer Fellowships

Three Stanford Medicine students have been named to the 2015-16 class of San Francisco Bay Area Albert Schweitzer Fellows. The fellows will spend a year learning about and completing community service projects while pursuing their individual academic paths and developing leadership skills. Each fellow will receive a $2,000 stipend.

Following are names of the Stanford medical students and their projects:

• Gunsagar Gulati will develop a health-coaching and education program for patients at Santa Clara Valley Medical Center Milpitas.

• Jecca Steinberg plans to help pediatric preschool-age patients at Fair Oaks Clinic in Redwood City prepare for school.

• Paula Trepman will work with the Boys & Girls Clubs of the Peninsula to teach elementary school students healthy habits using dance and nutrition education. **ISM**