INSIDE STANFORD MEDICINE

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More than 500 people attended this year's Big Data in Biomedicine Conference.

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Stem cells help stroke patients, study finds

By Bruce Goldman

Injecting modified, human, adult stem cells directly into the brains of chronic stroke patients proved not only safe but effective in restoring motor function, according to the findings of a small clinical trial led by School of Medicine investigators.

The patients, all of whom had suffered their first and only stroke between six months and three years before receiving the injections, remained conscious under light anesthesia throughout the procedure, which involved drilling a small hole through their skulls; the next day they all went home.

Although more than three-quarters of them suffered from transient headaches afterward — probably due to the surgical procedure and the physical constraints employed to ensure its precision — there were no side effects attributable to the stem cells themselves, and no life-threatening adverse effects linked to the procedure used to administer them, according to a paper, published online June 2 in *Stroke*, that details the trial's results.

Sonia Olea Coontz, of Long Beach, California, was one of those patients. Now 36, Coontz had a stroke in 2011. She enrolled in the Stanford trial after finding out about it during an online search.

"My right arm wasn't working at all," said Coontz. "It felt like it was almost dead. My right leg worked, but not well." She walked with a noticeable limp. "I used a wheelchair a lot." Not anymore, though.

"After my surgery, they woke up," she said of her limbs.

The promising results set the stage for an expanded trial of the procedure that is now getting underway. They also call for new thinking regarding the permanence of brain damage, said Gary Steinberg, MD, PhD, professor and chair of neurosurgery. Steinberg, who has more than 15 years' worth of experience in work with stem cell therapies for neurological indications, is the paper's lead and senior author.

MARK RIGHTMIRE

Sonia Olea Coontz had a stroke in 2011 that affected the movement of her right arm and leg. After modified stem cells were injected into her brain as part of a clinical trial, she says her limbs "woke up."

'Clinically meaningful' results

"This was just a single trial, and a small one," cautioned Steinberg, who led the 18-patient trial and conducted 12 of the procedures himself. (The rest were performed at the University of Pittsburgh.) "It was designed primarily to test the procedure's safety. But patients improved by several standard measures, and their improvement was not only statistically significant, but clinically meaningful. Their ability to move around has recovered visibly. That's unprecedented. At six months out from a stroke, you don't expect to see any further recovery."

Some 800,000 people suffer a stroke each year in the United States alone. About 85 percent of all strokes are ischemic: They occur when a clot forms in a blood vessel supplying blood to part of the brain, with subsequent intensive damage to the affected area. The specific loss of function incurred depends on exactly where within the brain the stroke occurs, and on its magnitude.

Although approved therapies for ischemic stroke exist, to be effective they must be applied within a few hours of the event — a time frame that often is exceeded by the amount of time it takes for a stroke patient to arrive at a treatment center.

Disabling effects of stroke

Consequently, only a small fraction of patients benefit from treatment during the stroke's acute phase. The great majority of survivors end up with enduring disabilities. Some lost functionality often returns, but it's typically limited. And the prevailing consensus among neurologists is that virtually all recovery that's going to occur comes within the first six months after the stroke.

"There are close to 7 million chronic stroke patients in the United States," Steinberg said. "If this treatment really works for that huge population, it has great potential."

For the trial, the investigators screened 379 patients and selected 18, whose average age was 61. For most patients, at least a full year had passed since their stroke — well past the time when further recovery might be hoped for. In each case, the stroke had taken place beneath the brain's outermost layer, or cortex, and had severely affected motor function.

"Some patients couldn't walk," Steinberg said. "Others See STROKE, page 7

'Design thinking' class aims to improve emergency-room patient experience

By Sara Wykes

Stan Nowak, PhD, a physicist at the SLAC National Accelerator Laboratory, typically spends his days using X-ray spectroscopy to understand the chemical and electronic properties of matter. But on a recent Saturday afternoon, he played the role of the estranged father of a fictional young woman brought into a simulated version of Stanford Hospital's emergency department after an automobile accident.

NORBERT VON DER GROEBEN

Winnie Liang and Stan Nowak take a two-day "design thinking" class on improving the emergency department's patient experience.

The patient — actually a high-tech mannequin voiced by a woman in a nearby control room — was conscious on a gurney. "Oh, it hurts," she said. "Ow, that really hurts!"

Ten genuine Stanford doctors, nurses and technicians provided simulated care to simulated patients.

The exercise was part of a two-day course in design thinking offered by the Hasso Plattner Institute of Design at Stanford, known informally as the d.school. Nowak was among the 14 students in the class. Their goal was go find ways to improve the patient experience in the hospital's emergency department. For the exercise, they played patients and their family members to get a sense of what it actually feels like to be in the often-chaotic atmosphere of an emergency department.

Empathy is a key element of design thinking, a step-by-step approach to problem-solving that involves observing and interviewing See DESIGN, page 6

Carla Shatz awarded Kavli Neuroscience Prize

Carla Shatz, PhD, professor of neurobiology and of biology at Stanford, has won the 2016 Kavli Neuroscience Prize for her work in understanding how the brain's wiring takes shape during development.

Carla Shatz

She was one of two Kavli Prize winners from Stanford announced on June 2. The other was Calvin Quate, PhD, emeritus professor of electrical engineering and of applied physics, who won the Nanoscience Prize for the invention of atomic force microscopy.

"Carla Shatz and Calvin Quate are pioneers in their fields, and the Kavli Prize reflects the significance of their groundbreaking contributions that have advanced our knowledge of neuroscience and nanoscience," said Stanford President John Hennessy. "For Stanford to have dual winners is an extraordinary honor and affirms the wide-ranging impact of the interdisciplinary research being done at the university."

The Kavli Prizes are awarded every other year in the areas of astrophysics, nanoscience and neuroscience. The prize is a partnership See SHATZ, page 7

Palliative, hospice care lacking among dying cancer patients

By Becky Bach

Medical societies, including the American Society of Clinical Oncology, recommend that patients with advanced cancer receive palliative care soon after diagnosis and receive hospice care for at least the last three days of their life. Yet major gaps persist between these recommendations and real-life practice, a new study shows.

Risha Gidwani, DrPH, a health economist at Veterans Affairs Palo Alto Health Economics Resource Center and a consulting assistant professor of medicine at the School of Medicine, and her colleagues examined care received by all veterans over the age of 65 with cancer who died in 2012, a total of 11,896 individuals.

The researchers found that 71 percent of veterans received hospice care, but only 52 percent received palliative care. They also found that exposure to hospice care differed significantly between patients treated by the U.S. Department of Veterans Affairs and those enrolled in Medicare. In addition, many patients who received palliative care received it late in their disease's progression rather than immediately following diagnosis, as recommended by ASCO.

Gidwani is the lead author of the study, which was published online May 27 in the *Journal of Palliative Medicine*. The senior author is Vincent Mor, PhD, a professor of health services, policy and practice at Brown University.

Risha Gidwani

Hospice, palliative care differences

Hospice and palliative care are often confused, but they are two distinct services, Gidwani explained. Palliative care is intended to alleviate symptoms and improve quality of life, and is appropriate for all patients with serious illness, not just those who are at the end of life. Conversely, hospice care is end-of-life care, which can also provide social support for family members. Physicians can recommend hospice care only if they believe the patient has fewer than 180 days to live.

"The main lesson learned is we need to improve exposure to palliative care, both in terms of how many patients receive it and when they receive it," Gidwani said. The team's analysis of palliative care focused on care provided by the VA because palliative care is not coded consistently in Medicare. However, the researchers could examine hospice care in both environments. When they compared the timing and provision of hospice care between patients treated by the VA and those who received care paid for by Medicare, they discovered differences that could not be explained by cancer types. For example, patients receiving VA care were less likely to receive hospice care for the minimum recommended three days compared with those in Medicare or in other contracted care paid for by VA. VA patients first received hospice care a median of 14 days before death, compared with patients in VA-contracted care who entered hospice a median of 28 days before death.

"Ideally, there shouldn't be any difference in timing of this care," Gidwani said. "Patients should receive a service based on their clinical need, not due to healthcare system factors."

Hospice care policies differ

Interestingly, Medicare and the VA have different policies on the use of hospice care; VA cancer patients can continue receiving curative treatment while in hospice care, but Medicare patients must stop any chemotherapy or radiation before beginning hospice. However, nearly 70 percent of VA patients stopped curative treatment before entering hospice, even though they didn't need to, Gidwani said. She and colleagues are planning future research to understand why.

The team also found differences in the use of hospice and palliative care between cancer types and ages. Patients with brain cancer were more likely to receive palliative care than those with kidney cancer, for example. In addition, patients older than 85 were less likely to receive palliative care than patients between the ages of 65 and 69. But patients older than 80 were more likely to receive hospice care than younger patients. Those with brain cancer, melanoma or pancreatic cancer were more likely to receive hospice than patients with prostate or lung cancer.

"Our work indicates palliative care needs to be better integrated into standard oncological care and that there is wide variation in receipt of hospice care. The VA is strongly supportive of palliative care and hospice, so it's possible that other non-VA environments are performing even worse with respect to appropriate receipt of hospice and palliative care for cancer patients," Gidwani said.

The research did uncover some positive findings, said VJ Periyakoil, MD, clinical associate professor of medicine at Stanford and director of the Stanford Palliative Care Education and Training Program, who was not involved with the study.

"The authors found that 85.6 percent of veterans had some exposure to hospice care or palliative care in the approximately 180 days before death. This is a much higher percentage than what we see in the community," Periyakoil said. The higher number is likely due to the size of the VA and its commitment to improving the care for seriously ill veterans, she said.

LIGHTHUNTER / SHUTTERSTOCK.COM

A new study reveals that only about half of veterans diagnosed with advanced cancer received palliative care.

However, the study highlights opportunities to improve access to care for patients older than 85, who are likely to have several medical ailments, Periyakoil said. In addition, the study's findings on palliative care are worrisome.

"We know that early palliative care increases both longevity and quality of life. It is really puzzling as to why patients are referred so late despite compelling data to do otherwise," she said. "Some doctors may say that they are unsure about the prognosis and that is why they refer patients late. However, that argument does not hold water as earlier referrals are better, and at worst we would be guilty of referring a patient a little earlier in the trajectory."

Another Stanford-affiliated co-author of the study is Todd Wagner, PhD, a fellow at Stanford's Center for Health Policy and Center for Primary Care and Outcomes Research. He is also the associate director of the VA Health Economics Resource Center and of the VA Center for Innovation to Implementation.

Researchers affiliated with the University of Pennsylvania, Providence VA Medical Center, Philadelphia VA Medical Center, Eastern Colorado VA Healthcare System and Brown University also co-authored the study.

The study was funded by the U.S. Department of Veterans Affairs. ISM

Study provides insight into bacterial resilience, antibiotic targets

By Nicholas Weiler

Researchers at Stanford and UC-San Francisco have performed the first comprehensive survey of the central genes and proteins essential to bacterial life.

The study, which combined a new variant of CRISPR gene-editing technology with automated cell imaging, generated a new understanding of the fundamental gene networks that make bacteria so resilient to environmental stress and, increasingly, to antibacterial drugs. The research also demonstrated a practical approach to identifying the mechanism of action of potential new antibiotic compounds, which the researchers hope can be harnessed to aid the design of better drugs to fight a growing epidemic of antibiotic resistance.

Most of the core aspects of complex life, such as how cells copy their DNA, reproduce and make key proteins and membranes, are based on the same genes and protein machinery found in simple, single-celled bacteria. But even in bacteria, how all these proteins work together to power life is only partly understood. In the new study, published online May 26 in *Cell*, researchers developed a new approach to understanding what makes bacteria tick.

"Previously, genetic study of the most essential genes for life was very challenging," said Carol Gross, PhD, professor of cell and tissue biology and of microbiology and immunology at UCSF's School of Dentistry.

Gross shares senior authorship of the study K.C. Huang, PhD, associate professor of bioengineering and of microbiology and immunology at Stanford; and Stanley Qi, PhD, assistant professor of bioengineering and of chemical and systems biology at Stanford.

The lead authors are UCSF postdoctoral scholar Jason Peters, PhD, and Stanford graduate students Alexandre Colavin and Handuo Shi.

'Knockdowns'

Geneticists often learn about a gene's function by experimentally switching off a gene and observing what happens to the cell in what is called a "knockout" experiment, Gross said. "The problem with studying the most fundamental genes, though, is that you can't knock them out — the cells would just die."

The study relied on a new technique that allowed the researchers to instead generate "knockdowns" of each gene of interest. Unlike a knockout's binary on-off switch, a knockdown experiment essentially places a volume knob on each gene to gently turn down how much protein a cell makes. This way, the researchers could turn down an essential gene's activity just enough to examine its importance in a cell's daily activities, but not enough to kill the cell outright.

The technique, called CRISPR interference, CRISPRi, was recently developed by Qi. CRISPRi technology is quite different from the CRISPR-Cas9 techniques that are increasingly used by genetic engineers as a simple tool for cutting and splicing DNA: Instead of modifying DNA, CRISPRi precisely tunes cells' production of specific proteins.

The researchers used CRISPRi to systematically knock down the production of each of 258 essential proteins in the bacterium Bacillus subtilis, one gene at a time, and then observed how the cellular machinery performed in this weakened state using high-throughput, computer-controlled microscopy developed by Huang's lab.

For the vast majority of essential proteins, the researchers found, a complete loss of the protein produced major disruptions to the cells' integrity: deforming their normal shape or causing them to burst open and sabotaging cell division or simply halting growth altogether. By contrast, using CRISPRi to partially deprive the cells of these proteins produced subtler changes, and revealed that the essential proteins fell into two classes: those that changed cell shape through direct control **See KNOCKDOWNS, page 3**

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STANFORD MEDICINE

Artificial muscle fibers help keep muscle stem cells potent in lab

By Krista Conger

There's no place like home — particularly if you're a muscle stem cell.

Snuggled comfortably along the length of our muscle fibers, these stem cells rest quietly, biding their time until the muscle needs to be repaired after injury. Although it's possible to maintain muscle stem cells in a laboratory dish, they're not really happy there. Within a short time they begin to divide and lose their ability to function as stem cells.

Now researchers at the School of Medicine have come up with a way to create a home away from home for the stem cells in the form of artificial muscle fibers. They've also identified the particular "soup" of molecules and nutrients necessary to keep the cells in their most potent, regenerative state.

"Normally these stem cells like to cuddle right up against their native muscle fibers," said Thomas Rando, MD, PhD, professor of neurology. "When we disrupt that interaction, the cells are activated and begin to divide and become less stemlike. But now we've designed an artificial substrate that, to the cells, looks, smells and feels like a real muscle fiber. When we also bathe these fibers in the appropriate factors, we find that the stem cells maintain high-potency and regenerative capacity."

Why happiness matters

Keeping muscle stem cells happy in the lab is an important step toward potential therapies for conditions like muscular dystrophy and toward regenerating missing muscle after an injury. One day researchers would like to be able to remove a patient's own muscle stem cells, correct any genetic deficiencies if necessary, and then transplant the cells back into the patient to regenerate healthy muscle tissues. This is not possible if the stem cells lose their ability to regenerate new muscle.

The researchers conducted most of their experiments in mice, using muscle stem cells from the animals. However, they were also able to show that human muscle stem cells remained more potent and could be more efficiently transplanted into laboratory mice when grown under similar conditions.

A paper describing the research was published online May 30 in *Nature Biotechnology*. Rando is the senior author. Former postdoctoral scholar Marco Quarta, PhD, is the lead author.

In order to prevent newly isolated muscle stem cells from activating when maintained in the laboratory, the researchers sought to identify genes whose expression increased when the cells begin to divide. Those genes, they reasoned, were likely to be involved in nudging the cells out of their potent, quiescent state and into a proliferative, less-stemlike state. Conversely, they also identified genes that were highly expressed in the quiescent cells.

Thomas Rando

Testing compound combinations

Once they had determined the gene-expression profiles unique to quiescence and activation, they tested various combinations of 50 compounds previously known or suspected to promote cell quiescence — adding them to the broth in which the cells were grown and watching whether the cells began to express genes involved with activation and to divide, or whether they continued to express the quiescence-associated genes. Eventually, the researchers came up with a panel of compounds that helped keep the cells potent over a period of about 48 hours.

Another key component of regenerative therapy is the ability of the quiescent stem cells to begin dividing after transplantation when they receive the appropriate triggers. Quarta and Rando found that growing the cells in the newly created broth for more than about three days compromised their ability to begin dividing when they were exposed to a combination of factors that normally promote growth. They speculated that the cells also needed the specialized environment of the muscle fiber to be optimally responsive to growth signals and to maintain their ability to reconstitute muscle tissue on demand.

A muscle fiber surrogate

Quarta and Rando joined forces with colleagues in Stanford's Department of Materials Science and Engineering to figure out a way to assuage the homesick stem cells' need for a muscle fiber to cling to. They needed the surrogate to be as close to the real thing as possible to prevent the cells from activating and losing their special stem cell properties. Ideally, it would have elasticity similar to real muscle fibers.

The researchers found that they could create elastic, artificial muscle fibers out of a naturally occurring, biocompatible molecule called collagen 1 by extruding it from a minipump to mimic the shape and geometry of a real muscle fiber.

"The process itself is quite simple," said Rando. "The collagen extrusion device makes it easy and scalable. We can adjust the stiffness and size of the fibers, and then coat them with proteins we know are present in native muscle fibers."

When the researchers applied muscle stem cells to the artificial collagen fibers, the cells quickly "homed" to places similar to those in which they would be found in real muscle. When maintained in the specially concocted quiescence broth, the cells appeared snug and happy along the collagen fibers. Furthermore, transplantation experiments indicated the muscle stem cells maintained their potency over several days and were able to quickly engraft and begin making new tissue in recipient animals.

The researchers also repeated the experiment using human muscle stem cells maintained under similar conditions and then transplanted into laboratory mice.

"This artificial niche, plus bathing the cells in the appropriate factors, allows us to maintain the cells in a highly potent, quiescent state," said Rando. "Now we can genetically engineer stem cells, transplant them back into the animal and see that they are effective in engrafting and making new tissue."

Other Stanford authors of the study are graduate student Jamie Brett; former graduate student Rebecca DiMarco, PhD; postdoctoral scholars Antoine De Morree, PhD, and James Su, PhD; former postdoctoral scholar Stephane Boutet, PhD; research associates Robert Chacon, Victor Garcia and Michael Gibbons; professor of cardiothoracic surgery Joseph Shrager, MD, and associate professor of materials science and engineering Sarah Heilshorn, PhD.

The research was supported by the Glenn Foundation for Medical Research, the National Institutes of Health, the California Institute for Regenerative Medicine and the Department of Veterans Affairs.

Stanford's Department of Neurology and Neurological Sciences also supported the work. ISM

Knockdowns

continued from page 2

of the bacterial cell wall, and modulators that affected cell shape through indirect mechanisms.

"These findings reveal a new set of failure modes that can be targeted by antibiotics and demonstrate how cells have evolved to couple their systems together to avoid these fates," said Huang.

Stressing cells

The team also subjected each knockdown to more than 100 different stresses, such as dosing them with antibiotics or varying their nutrient supply. By analyzing nearly 30,000 combinations of essential protein knockdowns and environmental stressors, the team characterized the importance of the different essential proteins for coping with particular environmental stressors, and observed a number of key principles of bacterial resilience. They also showed that the technique has the potential to be used to identify the biological mechanisms of new antibiotic compounds.

> "Previously, genetic study of the most essential genes for life was very challenging."

To test their approach as a platform for drug discovery, the researchers demonstrated that the knockdown of a particular enzyme important for building bacterial cell walls made cells uniquely susceptible to an antibiotic whose mode of action was previously unknown. Such experiments, the team said, highlight the power of studying all essential genes at once, an approach they say could be an efficient way to characterize targets of other antibiotic drugs, which is a major bottleneck in the transfer of drugs from the lab to the clinic.

Other experiments illustrated that bacterial cells have evolved many redundancies — such as producing more of each critical protein than they need as a rainy-day supply for times of starvation. The researchers learned that bacteria also have backups for many essential proteins, a fail-safe mechanism that allows them to better withstand genetic mutations or pharmacological attacks.

For example, one experiment focused on three proteins known to play critical roles in creating bacterial cells' protective outer layer, a vital process that is targeted by several of the most effective current antibiotics.

"We turned down the first protein from full blast to zero, and the cells were fine," Gross said. "We did the same for the second protein and still things were fine. We had to knock down all three proteins before the cell died. So while the process is essential, each protein was not."

The team went on to discover dozens of pairs of proteins with seemingly unrelated functions that provide similar levels of resilience to environmental stresses, suggesting that cells have redundant backup systems for dealing with disruptions to key systems.

'Optimized to survive adversity'

"In a way, these experiments allowed us to reverse-engineer evolution by observing its results across every living process," Huang said. "Our findings suggest that cells are optimized to survive adversity. It makes sense given that often during bacterial evolution, nutrients would have been in short supply and environmental conditions harsh. Therefore, the essential genes and proteins would have evolved so that cells survive in times of scarcity."

Other researchers from UCSF, as well as researchers from UC-Berkeley and McMaster University in Ontario, also contributed to the study.

This work received major support from the UCSF Center for Systems and Synthetic Biology, a Stanford Graduate Fellowship and a Stanford Agilent Fellowship, the Canadian Institutes of Health Research and a Canada Research Chair, the National Institutes of Health, the Howard Hughes Medical Institute and the National Science foundation.

The Stanford departments of Bioengineering, of Microbiology and Immunology and of Chemical and Systems Biology also supported the work. The Department of Bioengineering is jointly operated by the School of Medicine and the School of Engineering. ISM

Two professors elected to National Academy of Sciences

School of Medicine faculty members Helen Blau, PhD, and John Boothroyd, PhD, have been elected to the National Academy of Sciences.

They were formally inducted in April to the academy, which was created in 1863 to advise the nation on issues related to science and technology. Scholars are elected to the academy in recognition of their outstanding contributions to research.

The academy also elected seven other Stanford faculty members to its ranks this year.

Helen Blau

Blau is the Donald E. and Delia B. Baxter Foundation Professor and a professor of microbiology and immunology. She directs the Baxter Laboratory for Stem Cell Biology. Her research has uncovered regulatory networks controlling nuclear reprogramming and therapeutic agents to enhance muscle regeneration in aging and dystrophy.

Boothroyd is the Burt and Avery Professor of Immunology, a professor of microbiology and immunology, and the associate vice provost for graduate education. His research focuses on how the intracellular parasite, *Toxoplasma gondii*, causes disease in the developing fetus and in those who are immunocompromised though AIDS, cancer or transplantation. ISM

John Boothroyd

Big data conference builds foundation for precision health

By Jennie Dusheck

The movement to revolutionize health care and promote populationwide wellness will depend on melding diverse kinds of data from people in every corner of the globe, several speakers said at Stanford Medicine's fourth annual Big Data in Biomedicine Conference.

Lloyd Minor, MD, dean of the School of Medicine, opened this year's conference —titled "Enabling Precision Health" — by noting that, "Without big data, there is no precision health. Data makes possible everything that precision health promises — true patient-centered care based upon prediction and prevention rather than relying exclusively on diagnosis and treatment."

The conference, held May 25-26 at the Li Ka Shing Center for Learning and Knowledge, drew some 500 attendees and more than 2,100 remote viewers.

Now that the era of big data has arrived, breaking down barriers and looking for ways to exploit the rich interactions at the boundaries between different kinds of data — such as the particular mix of bacteria in the gut and the self-reported status of a person's health and mood — is attracting attention. "Innovation," said Claudia Williams, MS, senior advisor for health technology and innovation at the White House Office of Science and Technology Policy, "often comes at edges."

Turning patients into partners

That can include policy changes such as tax credits for people who donate their data or finding ways to allow patients themselves to generate innovations. Williams talked extensively about making patients partners in research; for example, she talked about a parent who tracked her child's symptoms over time, noting which antibiotics had what effects on which symptoms. Such a parent might work well with a physician willing to look at that information and add other data from the child's medical records into the mix.

"We focus a lot on motivating patients to share data," Williams said, "and less on feedback loops and friction points." One friction point is that patients can't always get the data they themselves provided. Patients are legally entitled to receive all of their data in any form they request, said Williams. She advocates making that process easier and requiring healthcare providers to comply more consistently.

Another major source of new data is biobanks, which Rohit Gupta, director of the Spectrum Biobank at Stanford, said are more than just freezers full of samples. "A sample's purpose is to produce data." And that data should include the information in the samples themselves and the information about the patients — all integrated into a single database.

The power of biobanks

Some in the audience audibly sighed covetously when Oxford professor of medicine and epidemiology Martin Landray, PhD, described how the UKBiobank database contains both specimens and associated self-reports from hundreds of thousands of individuals. Landray was asked procedural questions about how easy it was for researchers to obtain data from the UKBiobank and estimates of how long it took to obtain the data.

Then, just a couple of hours later at the conference, Kathy Hudson, PhD, deputy director for science, outreach and policy at the National Institutes of Health, announced a $142 million grant to establish the world's largest research biobank at the Mayo Clinic in Minnesota, as part of President Obama's Precision Medicine Initiative. The new biobank will collect samples and information from 1 million individuals as part of the PMI Cohort program.

In a panel discussion on genomics, Carlos Bustamante, PhD, professor of genetics and of biomedical data science at Stanford, and other speakers agreed on the importance of broadening genomic databases to include people from all over the world, not just those of primarily European descent, as is now the case.

The future of big data and precision health is all about bringing together many kinds of data from many kinds of people, and about sharing data among patients as well as researchers. As Minor later said, "data is the ultimate rocket fuel that will launch us to the exciting and unchartered universe of proactive, predictive and precise health care." **ISM**

PHOTOS BY SAUL BROMBERGER

(Top) Mark Cullen, far left, moderates a panel on population health at the Big Data in Biomedicine Conference. Euan Ashley (above) talks with Claudia Williams of the White House Office of Science and Technology Policy.

(Above) More than 500 people attended the May 24-25 conference, and another 2,100 watched the events online. (Left) Lloyd Minor, dean of the School of Medicine, welcomes conference attendees.

New paper addresses the meaning of 'research reproducibility'

By Jennie Dusheck

The journal *Nature* recently published the results of a survey that asked scientists if they thought the published scientific literature is mostly correct.

The exact question they asked nearly 1,600 scientists in fields ranging from physics to biomedicine was, "How much published work in your field is reproducible?" Many scientists who answered the survey tended to be quite confident in their field's literature even though numerous studies have shown reproducibility as low as 11 percent in some fields. Three-quarters of the researchers thought that at least half of the papers published in their field would be reproducible.

But it's not just Pollyannaish optimism that is the problem, say three researchers from the Meta-Research Innovation Center at Stanford, known as METRICS. It turns out that "reproducibility," "replicability" and several other terms are not used consistently in scientific communication. To fix the flaws of science, everyone needs to use such terms more thoughtfully and with precision, the researchers wrote in a paper titled "What does research reproducibility mean?" that was published June 2 in *Science Translational Medicine.*

The three authors of the paper are Steven Goodman, MD, PhD, professor of medicine and of health research and policy at Stanford; Daniele Fanelli, PhD, a senior research scientist at METRICS; and John Ioannidis, MD, DSc, professor of medicine and of health research and policy at Stanford. They make the case that even if we define and use terms such as "reproducibility," "replicability," "reliability," "robustness" and "generalizability" consistently and correctly, what researchers are really after is the truth.

The paper said that "treating reproducibility as an end in itself — rather than as an imperfect surrogate for scientific truth — is partly responsible for the current terminological and operational morass, as well as how we can benefit by refocusing on cumulative evidence and truth."

The paper included an amusing table of terms for misleading practices in science, including torturing, data snooping and P-hacking.

"We need," the authors wrote, "to move toward a better understanding of the relationship between reproducibility, cumulative evidence and the truth of scientific claims." **ISM**

Study shows different brain cells process positive, negative experiences

By Andrew Myers

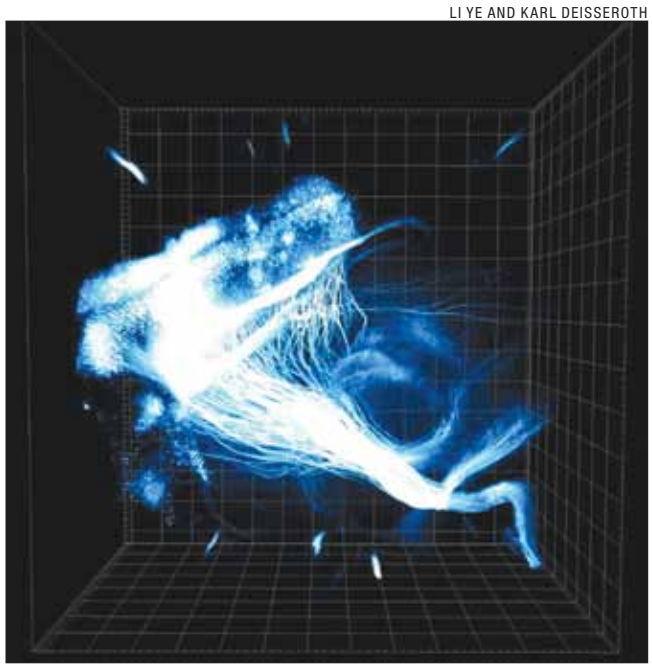
The prefrontal cortex plays a mysterious yet central role in the mammalian brain. It has been linked to mood regulation, and different cells in the prefrontal cortex seem to respond to positive and negative experiences. How the prefrontal cortex governs these opposing processes of reward or aversion, however, has been largely unknown.

In a new paper published online May 26 in *Cell,* researchers at Stanford, led by Karl Deisseroth, have united two transformational research techniques to show how the prefrontal circuits that process positive and negative experiences are distinctly and fundamentally different from one another, both in how they function and in how they are wired to other parts of the brain.

"These cells are built differently," said Deisseroth, MD, PhD, professor of bioengineering and of psychiatry and behavioral sciences. "They didn't start the same and then change their nature with recent experience. They appear wired specifically to communicate positive or negative experience."

This has deep implications for both our understanding of how reward and aversion work, but also for the potential development of drugs or other therapies to treat drug addiction and mental illnesses tied to reward and aversion.

LI YE AND KARL DEISSEROTH



This 3-D CLARITY image shows neural connections from the prefrontal cortex across an entire transparent mouse brain.

The full dream

The paper fully combines, for the first time, two novel research techniques developed by Deisseroth: optogenetics and CLARITY.

Optogenetics is a technique for genetically modifying cells — neurons, in this case — in living animals so that their function can be turned on and off with light. CLARITY is a remarkable feat of chemical engineering in which the fatty, opaque tissues that constitute an intact, non-living brain are removed, leaving behind a transparent physical structure with all of its parts and wiring exactly in place.

Karl Deisseroth

"Unifying optogenetics and CLARITY enables us to discover how behavior arises from whole-brain circuit activity patterns without losing sight of individual neurons," said Deisseroth, who holds the D. H. Chen Professorship. "We can obtain the fine detail and the big picture at the same time."

Previously it has not been possible, for example, to determine whether the neurons in the prefrontal cortex that are active during distinct experiences are physically different kinds of cells or whether they simply receive different information. This distinction matters a great deal when thinking about the basic processing in this part of the brain, as well as when considering possible therapies targeted to cell type.

Prior techniques allowed researchers to either listen in on the activity of a group of neurons using electrodes or to image brain activity. But these techniques can't report how these cells are connected across an individual subject's brain as researchers track cell activity during behavior.

Now, by uniting optogenetics and CLARITY, Deisseroth's team has shown how to study both the function and the wiring of neurons simultaneously, thus hitting a crucial target for the National Institutes of Health's BRAIN Initiative.

"This is a first look at these cells in detail while retaining the link to activity during behavior," Deisseroth said. "It's like getting to know the various components of a computer circuit, but also digging deeper into what their individual properties are, how they are wired together and how they are used in the circuit. Ultimately, it helps you understand how it all works."

Achieving CLARITY

The first facet of the research involved CLARITY. It allowed the researchers to trace specific pathways and "label" specific molecular structures within the brains of the subjects, which in this case were mice. The researchers gave the mice positive or negative stimuli. Only the neurons that had been strongly active during the experience became labeled — along with their outgoing connections — allowing effective tracing of the distinct circuits through the brain.

Using optogenetics, the researchers controlled specific neurons, within the living animals that had been active during positive or negative experiences. The team was able to then evaluate how those particular neurons affect behavioral outcomes.

Those mice had been optogenetically modified so that the cells becoming light-sensitive were only those that were most active during the positive or negative experience provided. For instance, the team was able to turn on only the positive-experience-associated cells to observe behavior in the mice. In effect, they were able to fool the mice into thinking they were experiencing a positive-valence stimulus, such as chocolate or cocaine, in order to observe how behavior changed.

By pairing the techniques in the same experiment, Deisseroth's team was able to determine not only that the molecular signature of the positive cells was different from those of the negative cells — both cocaine and chocolate associated with cells producing a particular molecular marker called NPAS4 — but also that the positive and negative cells were wired to distant places in the brain in fundamentally differing ways.

Given the strong linkage between the prefrontal cortex and various psychiatric illness, Deisseroth said this study opens the possibility in future studies to identify and target different cell types with diverse therapeutic approaches, including drugs or external stimulation techniques.

Deisseroth said the findings of this study, as with his other transformational work, are the result of a remarkable interdisciplinary effort. In this case, the team included Liqun Luo, PhD, a Stanford professor of biology whose lab developed a mouse line that was used for one of several different experience-dependent labeling strategies in the paper, and Jennifer McNab, PhD, a Stanford assistant professor of radiology who helped quantify the cellular pathways through the brain. The experimental work was led by postdoctoral scholar Li Ye, PhD, former postdoctoral scholar Kimberly Thompson, PhD, and graduate student William Allen. All three were lead authors of the paper.

"The Stanford community is an incredible place for interdisciplinary research," Deisseroth said. "The right people are always just a short walk away. This study and its implications are a testament to the value of that environment."

The research is supported in part by the National Institute of Mental Health, National Institute on Drug Abuse, the Wiegers Family Fund, the Howard Hughes Medical Institute, the U.S. Army Research Laboratory and the Defense Advanced Research Projects Agency.

Stanford's departments of Bioengineering and of Psychiatry and Behavioral Sciences also supported the work. The Department of Bioengineering is operated jointly by the School of Medicine and the School of Engineering. ISM

Drop-in help for mobile devices, laptops now available at medical school

By Rosanne Spector

The School of Medicine has quietly opened its own version of the Apple Genius Bar — but it's not only for Apple products.

Unlike the technicians at an Apple Store, the medical school's Tech Bar staff will tend to any smartphone, tablet or laptop you use for Stanford work, whether the maker is Apple, Microsoft, Samsung or none of the above. The free technical service, available to all students, staff and faculty at the School of Medicine, is open from 8 a.m. to 6 p.m. Monday through Friday on the lower level of Lane Medical Library.

Launched by Stanford's Office of Information Resources and Technology last month, the Tech Bar is holding its grand opening today, offering not only computer care but refreshments and giveaways.

No problems recruiting staff

IRT staff members have vied for the chance to be part of the seven-member computer Tech Bar team.

"We asked for volunteers from the help desk and field support staff, and we got an overwhelming response," said Kathy Fisher, a member of the field support staff who is helping to publicize the program. "We're planning on rotating every couple of months so everyone who wants to can work at the Tech Bar."

As part of the preparation to offer the service, a former Apple genius bar technician, Phillip Lochbaum — who is now a desktop analyst with Stanford IRT — helped train the Tech Bar team in the tricks of the trade.

"No one knows how to fix every problem, but you have a team you can turn to," said Lochbaum. One of the keys to a successful drop-in support desk is to know when to ask your teammates for help. The team is also building a database of solutions as they address each customer's problem.

Customer focus, empathy

Another key is to have both customer focus and empathy for those you're serving, said Lochbaum. To hone those skills, the Tech Bar staffers ran through hours of role-playing scenarios with IRT managers and other colleagues acting as faculty, students and staff having a wide range of problems with their laptops, smartphones or tablets

"We selected scenarios that were very challenging for them, and they did a great job," Lochbaum said.

NORBERT VON DER GROEBEN

At the Tech Bar in Lane Medical Library, service desk technician Michelle Dumalag-Perez installs updates on a laptop used by radiologist Michael Iv.

In addition to the Tech Bar service for mobile devices and laptops, IRT will continue to offer IT support through the existing channels: calling 725-8000 or submitting a ticket at https://irthelp.stanford.edu. ISM

Design

continued from page 1

people as they go through an experience, and then using that information to prototype and test ways of improving the product or process.

For example, before building a better toothbrush, a product designer would go into people's homes, watch them brush their teeth and ask them about the experience.

The emergency room experience

Design thinking "is a way for health care to make changes by empathizing with our patients and their families," said Alpa Vyas, Stanford Health Care vice president for patient experience. "We want to know what their unmet needs are. Our patients have told us they want us to know them and to understand them. Applying design thinking to health care is an invaluable way for us to do that."

The class's focus was on care in the emergency room — not the medicine, but the experience. Design thinking's process, which begins by asking people how they feel, is a good way to get to that type of information. "We know that if we control pain and take care of the medical emergency quickly, we are doing our job," said one of the class's teachers, Alexei Wagner, MD, MBA, a clinical instructor of emergency medicine, visiting lecturer at the d.school and assistant medical director of the Department of Emergency Medicine. "We wanted to know what else we could do."

Stanford junior Kinjal Vasavada, one of the class's 14 students, developed a new appreciation for how change could evolve in medicine. She had participated in other d.school classes, but she said that until she entered this one, she wasn't sure if she could find opportunities to apply design thinking to medicine, but "this class proved me totally wrong."

Interviewing patients, families

On the first day of class, the students interviewed patients and families about their experiences with medical care. Later that day, they took part in the exercise.

The simulation "added the value of walking in a patient's shoes, an emotional value that complemented the interviews," said Emilie Wagner, a design strategist who co-taught the class with Marney Boughan, another design strategist who trained with d.school co-founder David Kelley, the Donald W. Whittier Professor in Mechanical Engineering at Stanford.

"Suddenly, our students could empathize," Wagner said. "It's a tool that encourages students to step out of designing for themselves and trust the people they're designing for."

PHOTOS BY NORBERT VON DER GROEBEN

Richa Wadekar (front), Fiona Zhou (middle) and Justin Norden work together in a class on redesigning the patient experience in the emergency department.

That first day produced an abundance of material to guide the class' second day of prototyping: Certain themes were quickly evident. Patients wanted a regular flow of information to help them better understand what was happening, and they wanted to know that their care providers were communicating with one another. Coordinated and clear communication, they said, would do much to relieve their heightened anxiety and fear.

Design thinking for new hospital

The participants concluded the class by presenting their research and ideas to hospital administrators and emergency medicine professionals. With the support of S.V. Mahadevan, MD, associate professor and chair of emergency medicine, and Alison Kerr, vice president of operations at Stanford Health Care, "we are looking into some of the ideas that were presented," Alexei Wagner said. "I don't think that we'd be doing this if we hadn't had the class."

SHC administrators have also incorporated design thinking into planning the new Stanford Hospital, scheduled to open to patients in 2018.

Recently, SHC staff used design thinking to complete a plan to redesign two nursing units in the current hospital to serve only patients with cancer. "Patients and their families were involved from the start," said Helen Waters, a design and innovation leader with Stanford Health Care. "We wanted to know what they needed and what they felt was missing."

The process included seven months of conducting interviews and tabletop exercises and simulating actual work routines in the proposed layouts of the nursing units to be redesigned.

Design thinking is becoming more enmeshed in all aspects of SHC's workings, Vyas said. "We do a lot of teaching and training across the system," she said. "We also have a d.school faculty member consult with us on a regular basis. We are looking for ways to complement the other improvement efforts we are making through the Stanford Operating System," which is SHC's improvement and management system. **ISM**

Kent Lee and Kinjal Vasavada were among 14 students who participated in the class.

Grace Hunter talks with fellow students in the class, offered by the Hasso Plattner Institute of Design at Stanford.

Stanford Health Care seeks book and magazine donations

The Volunteer Resources Office at Stanford Health Care is asking for help in boosting its supply of current reading materials.

The office receives many requests each day from patients and families for magazines and books to help pass the time. Below are the guidelines for donated materials:

• Magazines: no religious or adult content and nothing older than January 2016, although the office will accept older issues of such publications as *The Smithsonian*, *The Atlantic Monthly* and *The New Yorker*.

• Books: any hard- or soft-cover books, with the exception of cookbooks, textbooks or boosk with religious or adult content.

Donations can be dropped off in Guest Services at the Volunteer Resources Office, located in Pavilion B, Level 1, Room H1130H.

A donation sticker will be placed over the mailing address to protect the privacy of those who donate reading materials. **ISM**

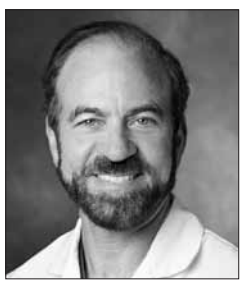
Stroke

continued from page 1

couldn't move their arm."

Into these patients' brains the neurosurgeons injected so-called SB623 cells — mesenchymal stem cells derived from the bone marrow of two donors and then modified to beneficially alter the cells' ability to restore neurologic function.

No immune rejection



Gary Steinberg

Mesenchymal stem cells are the naturally occurring precursors of muscle, fat, bone and tendon tissues. In preclinical studies, though, they've not been found to cause problems by differentiating into unwanted tissues or forming tumors. Easily harvested from bone marrow, they appear to trigger no strong immune reaction in recipients even when they come from an unrelated donor. In fact, they may actively suppress the immune system. For this trial, unlike the great majority of transplantation procedures, the stem cell recipients received no immunosuppressant drugs.

During the procedure, patients' heads were held in fixed positions while a hole was drilled through their skulls to allow for the injection of SB623 cells, accomplished with a syringe, into a number of spots at the periphery of the stroke-damaged area, which varied from patient to patient.

Afterward, patients were monitored via blood tests, clinical evaluations and brain imaging. Interestingly, the implanted stem cells themselves do not appear to survive very long in the brain. Preclinical studies have shown that these cells begin to disappear about one month after the procedure and are gone by two months. Yet, patients showed significant recovery by a number of measures within a month's time, and they continued improving for several months afterward, sustaining these improvements at six and 12 months after surgery. Steinberg said it's likely that factors secreted by the mesenchymal cells during their early postoperative presence near the stroke site stimulates lasting regeneration or reactivation of nearby nervous tissue.

No relevant blood abnormalities were observed. Some patients experienced transient nausea and vomiting, and 78 percent had temporary headaches related to the transplant procedure.

Motor-function improvements

Substantial improvements were seen in patients' scores on several widely accepted metrics of stroke recovery. Perhaps most notably, there was an overall 11.4-point improvement on the motor-function component of the Fugl-Meyer test, which specifically gauges patients' movement deficits.

"This wasn't just, 'They couldn't move their thumb, and now they can.' Patients who were in wheelchairs are walking now," said Steinberg, who is the Bernard and Ronni Lacroute-William Randolph Hearst Professor in Neurosurgery and Neurosciences.

> "We thought those brain circuits were dead. And we've learned that they're not."

"We know these cells don't survive for more than a month or so in the brain," he added. "Yet we see that patients' recovery is sustained for greater than one year and, in some cases now, more than two years."

Three years after her procedure, Coontz is jogging again. She now has full shoulder movement and "pretty good" elbow movement, and can make a fist, but her hand still isn't working well, she said. And what had been almost constant pain in her arm before the procedure ceased almost immediately afterward, she said. In addition, her enunciation, quite slurred prior to the procedure, has markedly improved since, according to a researcher who worked with her.

Importantly, the stroke patients' postoperative improvement was independent of their age or their condition's severity at the onset of the trial. "Older people tend not to respond to treatment as well, but here we see 70-year-olds recovering substantially," Steinberg said. "This could revolutionize our concept of what happens after not only stroke, but traumatic brain injury and even neurodegenerative disorders. The notion was that once the brain is injured, it doesn't recover — you're stuck with it. But if we can figure out how to jump-start these damaged brain circuits, we can change the whole effect.

"We thought those brain circuits were dead. And we've learned that they're not."

A new randomized, double-blinded multicenter phase-2b trial aiming to enroll 156 chronic stroke patients is now actively recruiting patients. Steinberg is the principal investigator of that trial.For more information, email stemcellstudy@stanford.edu.

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

Other Stanford co-authors of the study are Neil Schwartz, MD, PhD, clinical associate professor of neurology and neurological sciences and of neurosurgery; and former neurosurgery fellow Jeremiah Johnson, MD, now at the University of Texas Health Science Center in San Antonio.

The SB623 cells were provided by SanBio Inc., a biotechnology company based in Mountain View, California. SanBio also funded and helped in designing the trial, but did not participate in its execution.

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

Shatz

continued from page 1

among the Norwegian Academy of Science and Letters, The Kavli Foundation and the Norwegian Ministry of Education and Research. Winners of each prize will receive a gold medal and share $1 million, given during an awards ceremony in Oslo.

Shatz, who is the director of Stanford Bio-X, shares the Neuroscience Prize along with Eve Marder, PhD, of Brandeis University, and Michael Merzenich, PhD, of UC-San Francisco. Quate shares the Nanoscience Prize with Gerd Benning, PhD, a former member of IBM Zurich Research Laboratory, and Christoph Gerber, PhD, of the University of Basel.

Previous Stanford winners of the Kavli Prize include Thomas Sudhof, MD, the Avram Goldstein Professor in the School of Medicine, who went on to win the 2013 Nobel Prize in Physiology or Medicine; and Andrei Linde, PhD, the Harald Trap Friis Professor of Physics.

'Fire together, wire together'

Shatz learned of her prize the day before the official announcement immediately following the annual Shooter Lecture, which was given this year by Marder, her co-winner. "Eve had just given this incredible talk,and we were heading to a reception," Shatz said. That's when Shatz got a message to return an urgent phone call and learned of her award. She went back to the reception and encouraged Marder to return that same call.

Shatz has won a number of awards for her work and said each time it feels very precious.

"As a scientist I do what I do because I love going to work every day," she said. "Getting this kind of recognition in my field is an incredible gift and I feel very grateful."

She has spent her career focusing on understanding the changes that take place during the development of the brain, particularly the region that receives information from the eyes. This work has had implications for understanding learning and in neurodegenerative disease.

> "As a scientist I do what I do because I love going to work every day."

Her research uncovered mechanisms the brain uses to determine which of the myriad brain connections present before birth get strengthened and which are pruned to create our adult wiring. These same mechanisms are at play — albeit far less flexibly or frequently — throughout life. Her work revealed that as the brain develops, neurons that fire at the same time form stable connections. Those that fire out of sync lose their connections and get pruned back. This discovery led to the phrase, "Cells that fire together, wire together," along with, "Cells that fire out of sync, lose their link."

Shatz also pioneered the discovery that certain well-known proteins once believed to be in the exclusive employ of the immune system also moonlight in the brain, where they play a key role in detecting which neurons are firing out of sync and should be pruned back. In mouse models, she and her colleagues have shown that manipulating the availability of some of these proteins might be able to reverse brain damage that occurs in Alzheimer's disease and stroke.

L.A. CICERO

Carla Shatz celebrates her Kavli Neuroscience Prize with members of her lab on June 2.

"This was exciting because it was the first time anybody could show a role for these proteins in the brain," Shatz has said. She said at the time people thought her findings were incorrect, or that the immune system was controlling the way the circuits formed. In later work she was able to show that the proteins, called MHCs, were active in neurons.

An early interest in brain activity

Shatz received her undergraduate degree from Radcliffe College and then did her graduate work at Harvard, where she studied under David Hubel and Torsten Wiesel, the 1981 recipients of the Nobel Prize in Physiology or Medicine, who stimulated her lifelong interest in understanding how the brain's activity controls its wiring.

In 1976, Shatz became the first woman to earn a PhD in neurobiology from Harvard University. She joined the faculty of Stanford University in 1978, and then took a faculty position at UC-Berkeley in 1992. She returned to Harvard in 2000 as the first woman to chair its Department of Neurobiology. In 2007, she returned to Stanford to become the director of Stanford Bio-X, the landmark bioscience research effort that promotes interdisciplinary collaborations among life scientists, medical scientists, engineers, physicists and scholars in other disciplines.

Shatz has said that moving to Stanford and having a lab in the interdisciplinary Clark Center, which is a hub for Bio-X, has increased her collaborations and expanded the kinds of science she can do. "Now we have this fabulous collaboration with a serious immunology lab, and because of it we may be able to make new drugs that might even work to treat Alzheimer's one day," she has said.

Shatz, who is the Sapp Family Provostial Professor, is a past president of the Society for Neuroscience. She is also a member of the Stanford Neurosciences Institute, the American Academy of Arts and Sciences, the National Academy of Sciences, the Institute of Medicine, the Royal Society (London) and the American Philosophical Society. Among the numerous prestigious awards that she has won over the course of her career are the Gruber Prize (2015), the Sackler Prize (2013) and the Society for Neuroscience's Gerard Prize (2011). **ISM**

Writers Bruce Goldman, Amy Adams and Bjorn Carey contributed to this story.

5 QUESTIONS

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

Susan Swetter on choosing a sunscreen

In her nearly 20 years as director of the Pigmented Lesion and Melanoma Program at the Stanford Cancer Institute, Susan Swetter, MD, professor of dermatology, has been asked many times about sunscreen. Consumer Reports' *recent analysis of 60 sunscreens labeled as SPF 30 or higher showed that more than 40 percent aren't providing that level of protection.*

Swetter shared her thoughts with writer Sara Wykes on what to consider when choosing a sunscreen.

ARTONO / SHUTTERSTOCK.COM

1 Why is SPF important?

SWETTER: Sun protection factor, or SPF, was originally designed to measure sun protection from ultraviolet B rays, the primary cause of sunburn and skin cancer. Only in recent years has research shown that exposure to ultraviolet A rays is equally damaging to the skin, and its harmful effects have been seen in people exposed to high amounts of UVA and UVB radiation in indoor tanning booths. Without the warning signs of sunburn, UVA radiation penetrates the skin more deeply than UVB rays. UVA radiation contributes to skin photoaging — discoloration, wrinkling and sagging of the skin. It also passes through the ozone layer, clouds and window glass. UVA rays are also more plentiful than UVB because they are strong throughout the day and the year. While SPF values are generally easy for consumers to understand, they are not a good measure of UVA protection. Of even more concern is that of 60 sunscreen products recently tested by *Consumer Reports*, 28 (43 percent) failed to meet even the UVB protection claims on their labels. Because most consumers don't apply the recommended amount of sunscreen to achieve the advertised SPF rating, much of the sun protection a person thinks they're getting isn't really happening.

Susan Swetter

2 What does the broad-spectrum claim on a label tell me about the amount of UVA and UVB protection?

SWETTER: "Broad spectrum" is the rating designed by the FDA to ensure that a sunscreen filters both lower-wavelength UVB and higher-wavelength UVA radiation. That term can now only be used if UVA protection reaches a critical wavelength of 370 nanometers. That's a problematic number since the UVA spectrum extends all the way to 400 nanometers. Unfortunately, no sunscreens commercially available in the United States (except for 25 percent zinc oxide, which is totally opaque) provide "far UVA" protection. There are sunscreens available in Europe and Australia that include far more effective UVA-filtering ingredients, namely Tinosorb S and Tinosorb M. In fact, Australia and Europe have the most effective UV filters for sunscreen formulations, while the United States has the least. We have been waiting for a decade for the FDA to incorporate these more effective UV filters into sunscreens, but the process is stalled, despite the 2014 Sunscreen Innovation Act, which enabled quicker time frames for FDA reviews of sunscreen chemicals available outside of the United States.

3 How much sunscreen is enough?

SWETTER: Adults need about two to three tablespoons of sunscreen for the body and one teaspoon for the face. If you use a sunscreen spray, be sure to rub it in to your skin to provide an even layer. Avoid spraying directly to the face, which is not a safe practice. Remember that sunscreens are part of a sun protection package that should also include clothing, sunglasses and avoidance of exposure during the peak hours of sun. If your sunscreen isn't delivering the degree of protection claimed on its label, make sure you are applying enough of it. Consider using a higher SPF formulation (50+) and reapply after swimming or sweating. You can also reapply sunscreen every two hours or so, but once you feel the prickly sensation of a sunburn, using more sunscreen won't help, and you simply need to get out of the sun.

4 How effective are sunscreen products labeled as natural?

SWETTER: *Consumer Reports* reported that physical sunscreens (also called "natural," "mineral" or "organic") were the ones most likely to fail the SPF accuracy test. The active UV filtering ingredients for those products are typically micronized titanium dioxide or zinc oxide (or both). These do work to protect against UVB, but have a low SPF in themselves. To improve a sunscreen's filtration of UVB and UVA and to raise its SPF rating, chemicals (usually octinoxate) must be added. Higher-SPF mineral sunscreens need to contain higher levels of zinc oxide (which is generally not cosmetically acceptable) or additional UV-filtering chemicals. A minimum of 10 percent concentration zinc oxide and/or titanium dioxide may be helpful. In general, chemical sunscreens provide UV filtration that is superior to that of physical sunscreens. The most appropriate use of physical sunscreens is for children under age 2 and adults and children who have skin allergies to chemical sunscreens.

5 What do you consider the most effective ingredients in a sunscreen?

SWETTER: In the United States, all broad-spectrum sunscreens contain avobenzone, which meets the 370-nanometer critical wavelength test for UVA filtration. However, because it breaks down in the sun after 30 minutes or so, it needs to be stabilized with an additional UV filter, called octocrylene. Most dermatologists would prefer to see sunscreens with ingredients that offer protection through the entire UV spectrum and are safe to use. Sunscreens with that more-effective level of protection are available in other countries and will hopefully be approved in the United States soon. In the meantime, use chemical sunscreens that contain avobenzone and octocrylene. We recommend those with SPF 30 or higher because most people don't put on enough, and we now know that the sunscreen's SPF may be overrated. Apply often. This approach should go a long way to preventing sunburn and skin cancer, including the most deadly form, melanoma. ISM

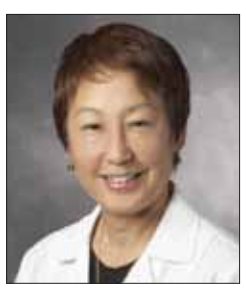
OF NOTE

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

Tej Azad

Maximilian Diehn

Michael Gardner



Judith Shizuru

Allison Kurian

Y. Joyce Liao

Jessica Pullen

Mackensie Yore

Shannon Stirman

Alice Ting

TEJ AZAD and **MAXIMILIAN DIEHN**, MD, PhD, have been awarded a $70,400 clinical research mentorship grant from the Doris Duke Charitable Foundation. The program was created to foster one-on-one mentorship between established scientists and medical students. Azad, an MD-MS student, and Diehn, an assistant professor of radiation oncology, plan to create a new method to detect circulating tumor DNA, using cancer personalized profiling by deep sequencing, to develop a liquid biopsy for pediatric sarcomas.

MICHAEL GARDNER, MD, was appointed professor of orthopaedic surgery, effective Jan. 1. He is chief of the orthopaedic trauma service and vice chair of clinical operations for the Department of Orthopaedic Surgery. He treats all aspects of fractures of the shoulder, elbow, lower extremity and pelvis. His research focuses on several molecular pathways involved in fracture healing, as well as the clinical outcomes of fracture treatment.

JUDITH SHIZURU, MD, PhD, was promoted to professor of medicine, effective Dec. 1, 2015. Her research focuses on understanding the cellular and molecular basis of resistance to bone marrow stem cell engraftment, and the translation of this basic biology to the development of clinical protocols that will improve the safety and broaden the use of this cellular therapy.

ALLISON KURIAN, MD, was promoted to associate professor of medicine and of health research and policy, effective Dec. 1, 2015. She directs the Stanford Women's Cancer Genetics Clinic. Her research focuses on identifying women at high risk of developing breast or gynecologic cancers, and on developing strategies for early cancer detection and prevention.

Y. JOYCE LIAO, MD, PhD, was promoted to associate professor of ophthalmology, effective Dec. 1, 2015. She directs the Stanford Neuro-Ophthalmology Program and the Human Ocular Motor Center. Her research focuses on vision loss and visual dysfunction related to optic neuropathies and eye movement disorders. She is also investigating key biomarkers of vision loss and studying treatments using neuroprotection, immune-based therapies and stem cell transplantation.

JESSICA PULLEN and **MACKENSIE YORE**, both medical students, have been named 2016-17 San Francisco Bay Area Schweitzer Fellows by the Albert Schweitzer Fellowship. The fellowship supports graduate students working to address unmet health needs in underserved communities while learning skills to become future leaders in health care. Pullen, a first-year student, will work with the Second Harvest Food Bank to increase access to healthy food and nutrition education for elementary school students in Santa Clara County. Yore, an MD-MS student, will work with the Ravenswood Family Health Center on a community fitness initiative in East Palo Alto.

SHANNON STIRMAN, PhD, was appointed assistant professor of psychiatry and behavioral sciences, effective Jan. 1. She is working to integrate evidence-based psychosocial interventions into public mental health-care systems.

ALICE TING, PhD, was appointed professor of genetics and of biology, effective Nov. 1, 2015. She develops technologies and molecular tools to study protein and RNA functions in living cells, with a focus on mitochondria and synapses. ISM