INSIDE STANFORD MEDICINE

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Researchers engineer yeast to produce non-narcotic cough suppressant.

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Integrated strategic plan unveiled at town hall

By Ruthann Richter

The world is entering a new era in biomedicine and health care, and Stanford Medicine can lead the the revolution toward proactive, precise health care with a unified, collective effort, Stanford Medicine's leaders said March 23 at a town hall meeting.

Lloyd Minor, MD, dean of the School of Medicine, and David Entwistle, president and CEO of Stanford Health Care, introduced an integrated strategic plan for the medical school and hospitals that constitute Stanford Medicine. The creation of this plan was a joint effort by Minor, Entwistle and Christopher Dawes, who recently retired as president and CEO of Lucile Packard Children's Hospital Stanford and Stanford Children's Health.

With more than 400 faculty, staff and students attending the event at the Li Ka Shing Center for Learning and Knowledge, Minor and Entwistle laid out the vision for a collaborative future that was developed by all three entities.

The integrated strategic plan has been nearly a year in the making, involving survey feedback from 4,000 members of the Stanford Medicine community and 120 interviews, as well as the recommendations of 13 working groups representing clinical and basic sciences, Stanford Health Care and Stanford Children's Health. It represents the first time the three entities have come together in this comprehensive way to chart a path for the future.

"The process itself brings us together as a community, … and in coming together, we've been able to achieve remarkable consensus and agreement on our mission and values," Minor said in a video shown at the meeting. "We face many external challenges and pressures in biomedicine and health care today, and in order to effectively address those challenges and be true to our mission and values, we have to have an integrated plan, and then we have to be able to execute on the plan."

Overarching principles

The plan to lead the biomedical revolution in precision health has two overarching principles: being human-centered and discovery-led. To be "human-centered" includes valuing not only patients but also students, trainees and other community members that Stanford Medicine touches. "Discovery-led" emphasizes the process of discovery, developing a wide-ranging base of knowledge about health and biomedical science and then using it to create new approaches to care that can be applied not only to patients at Stanford but around the world.

"The potential for what we can achieve in this plan is quite limitless," Entwistle said in the video. "You look at the innovative, technologically driven, research-driven organization that Stanford is. We have incredible breadth and opportunity. One of the challenges of an organization is there are always a lot of bright, shiny things out there we want to work on and do. The question is, can we pull together our collective resources and really be able to do a few things very well."

The plan calls for some sharing of resources, creating what Minor called "hubs of activity," where clinicians and researchers can work collaboratively on projects. He cited, as an example, the new cryoelectron microscopy hub at SLAC National Accelerator See PLAN, page 6

ROD SEARCEY

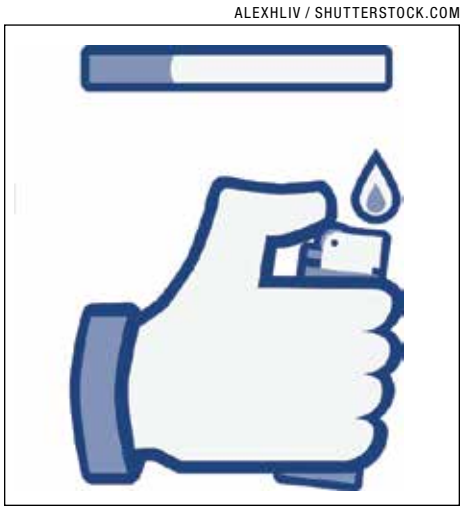
Dean Lloyd Minor and Stanford Health Care CEO David Entwistle discussed the integrated strategic planning effort at a March 23 town hall.

Promotion of tobacco products seen on Facebook, despite site's policies

By Amy Jeter Hansen

Tobacco products are marketed and sold through unpaid content on Facebook — in some cases, without regard for the age of potential buyers — despite policies from the social media company that restrict or prohibit the promotion of such items, researchers from the School of Medicine have found.

ALEXHLIV / SHUTTERSTOCK.COM



Although Facebook bars paid tobacco advertisements, a new study found extensive unpaid, or "organic," marketing, principally via brand-sponsored Facebook pages. In a comparison of the pages' content with Facebook policies covering commerce, page content and paid advertising, the study revealed numerous instances of apparent conflict with the rules or their spirit, though inconsistencies in and unexplained changes to some of the policies made it unclear exactly how those rules apply.

Among 108 company-sponsored pages for leading brands of cigars, e-cigarettes, hookah tobacco and smokeless tobacco, the study found more than half provided "shop now"-type buttons allowing users a way to buy their products. About two-thirds of the pages included sale promotions, such as coupons and discounts, and all but one featured imagery of a tobacco product. Though Facebook requires restricted access for people under 18 from pages promoting what it calls the "private sale" of regulated goods or services, See TOBACCO, page 7

Physical activity helps fight genetic risk of heart disease, new study finds

By Tracie White

Keeping fit, even if you're born with a high genetic risk for heart disease, still works to keep your heart healthy, according to a study led by researchers at the School of Medicine.

In one of the largest observational studies on fitness and heart disease, researchers examined data collected from nearly a half-million people in the UK Biobank database. They found that people with higher levels of grip strength, physical activity and cardiorespiratory fitness had reduced risks of heart attacks and stroke, even if they had a genetic predisposition for heart disease.

"People should not just give up on exercise because they have a high genetic risk for heart disease," said Erik Ingelsson, MD, PhD, professor of cardiovascular medicine. "And vice versa: Even if you have a low genetic risk, you should still get exercise. It all ties back to what we have known all along: It's a mix of genes and environment that influence health."

A paper describing the research was published online April 9 in *Circulation*. Ingelsson is the senior author. The lead author is Emmi Tikkanen, PhD, a former postdoctoral scholar at Stanford who is now senior data scientist at Nightingale Health Ltd. See FITNESS, page 6

AM-STUDIO / SHUTTERSTOCK.COM

Researchers discovered an association between high fitness levels and low levels of cardiovascular disease, even among those at genetic risk for it.

Telomerase-expressing liver cells found to regenerate the organ

By Krista Conger

Liver stem cells that express high levels of telomerase, a protein often associated with resistance to aging, act in mice to regenerate the organ during normal cellular turnover or tissue damage, according to a study by researchers at the School of Medicine.

The cells are distributed throughout the liver's lobes, enabling it to quickly repair itself regardless of the location of the damage.

Understanding the liver's remarkable capacity for repair and regeneration is a key step in understanding what happens when the organ ceases to function properly, such as in cases of cirrhosis or liver cancer.

"The liver is a very important source of human disease," said professor of medicine Steven Artandi, MD, PhD. "It's critical to understand the cellular mechanism by which the liver renews itself. We've found that these rare, proliferating cells are spread throughout the organ, and that they are necessary to enable the liver to replace damaged cells. We believe that it is also likely that these cells could give rise to liver cancers when their regulation goes awry."

Artandi is the senior author of the study, which was published online April 4 in *Nature*. Postdoctoral scholar Shengda Lin, PhD, is the lead author of the article.

A unique organ

The liver's cells, called hepatocytes, work to filter and remove toxins from the blood. The liver is unique among organs in its ability to fully regenerate from as little as 25 percent of its original mass. Chronic alcoholism or hepatitis infection can cause cycles of damage and renewal that lead to irreversible scarring that impairs the organ's function. But relatively little is known about how the organ regenerates, or which cells might be responsible for cancers.

"About 900,000 people die every year worldwide from cirrhosis," Artandi said, "and liver cancer is the fifth-leading cause of cancer death in the United States. But our understanding of how the liver renews itself has languished in comparison to advances made in other organs."

Telomerase is a protein complex that "tops off" the ends of chromosomes after DNA replication. Without its activity, protective chromosomal caps called telomeres would gradually shorten with each cell division. Most adult cells have little to no telomerase activity, and the progressive shortening of their telomeres serves as a kind of molecular clock that limits the cells' — and, some believe, an organism's — life span.

However, stem cells and some cancer cells make enough telomerase to keep their telomeres from shortening, effectively stopping the aging clock and allowing a seemingly unlimited number of cell divisions. Mutations that block telomerase activity cause cirrhosis in mice and humans. Conversely, mutations that kick telomerase into high gear are frequently found in liver cancers.

STEVE FISCH

Steven Artandi and his colleagues have found that some cells within the liver of mice express high levels of a protein that are key to the organ's ability to regenerate.

Lin and Artandi wondered whether they could use telomerase expression as a marker to identify the subset of cells responsible for regenerating the liver during normal turnover. These cells, they believe, could also serve as the cell of origin for liver cancer.

Making new cells

Lin found that, in mice, about 3-5 percent of all liver cells express unusually high levels of telomerase. The cells, which also expressed lower levels of genes involved in normal cellular metabolism, were evenly distributed throughout the liver's lobules. During regular cell turnover or after the liver was damaged, these cells proliferate in place to make clumps of new liver cells.

"These rare cells can be activated to divide and form clones throughout the liver," said Artandi, who holds the Jerome and Daisy Low Gilbert Professorship. "As mature hepatocytes die off, these clones replace the liver mass. But they are working in place; they are not being recruited away to other places in the liver. This may explain how the liver can quickly repair damage regardless of where it occurs in the organ."

> "You could imagine developing drugs that protect these telomerase-expressing cells."

The fact that these stem cells express fewer metabolic genes might be one way to protect the cells from the daily grind faced by their peers, and to limit the production of metabolic byproducts that can damage DNA.

"This may be one way to shelter these important cells and allow them to pass on a more pristine genome to their daughter cells," Artandi said. "They are not doing all the 'worker bee' functions of normal hepatocytes."

When Lin engineered the telomerase-expressing hepatocytes to die in response to a chemical signal and gave the mice with a liver-damaging chemical, he found that those animals in which the telomerase cells had been killed exhibited much more severe liver scarring than those in which the cells were functional.

"You could imagine developing drugs that protect these telomerase-expressing cells, or ways to use cell therapy approaches to renew livers," said Artandi. "On the cancer side, I think that these cells are very strong candidates for cell of origin. We are finally beginning to understand how this organ works."

Other Stanford authors are postdoctoral scholars Chandresh Gajera, PhD, Elisabete Nascimento, PhD, Lu Chen, PhD, and Patrick Neuhoefer, PhD; graduate student Alina Garbuzov; and assistant professor of ophthalmology Sui Wang, PhD.

The research was supported by the National Institutes of Health (grants CA197563 and AG056575), the Emerson Foundation and the California Tobacco-Related Disease Research Program.

Artandi is a member of Stanford Bio-X, the Stanford Cancer Institute and the Stanford Child Research Institute.

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

Scientists combine CRISPR, DNA barcoding to track cancer growth

By Ker Than

Stanford scientists have found a way to modify pairs of cancer-related genes in the lungs of mice and then precisely track individual cells of the resulting tumor — a technique that could dramatically speed up cancer research and drug development.

The work could finally allow scientists to mimic and then study the genetic diversity of cells found in tumors outside the lab.

"Human cancers don't have only one tumor-suppression mutation — they have combinations. The question is, how do different mutated genes cooperate or not cooperate with one another?" said Monte Winslow, PhD, professor of genetics and of pathology at the School of Medicine.

Just a few years ago, such a mapping study would have been a monumental, years-long effort. It would have required breeding several lineages of genetically modified mice, each with a different pair of inactivated tumor-suppressor genes. To explore all of the possible combinations, hundreds or thousands of mice would have been needed.

In contrast, Winslow and his colleagues conducted their experiments, which involved fewer than two dozen mice, in just a few months. "We've analyzed more genotypes of lung cancer tumors than the whole field has in 15 years," Winslow said.

Monte Winslow

Dmitri Petrov

A paper describing the technique was published online April 2 in Nature Genetics. Senior authorship is shared by Winslow and Dmitri Petrov, PhD, professor of biology and the Michelle and Kevin Douglas Professor in the School of Humanities and Sciences. Postdoctoral scholar Christopher McFarland, PhD, and former graduate student Zoë Rogers, PhD, are the lead authors.

A wild idea

The team achieved their results using CRISPR-Cas9 — a powerful gene-editing tool that can easily replace, modify or delete genetic sequences inside organisms — to create multiple, genetically distinct tumors in the lungs of individual animals. "We can induce thousands of clonal tumors in a single mouse," Winslow said.

However, in order to draw useful conclusions about the combinatory effects of different gene mutations, the scientists needed a precise way to label and track the growth of different tumors. Here again, conventional techniques, which involved trying to excise and compare the sizes of individual tumors, would have been insufficient.

"Not only was it extremely slow, but how do you pluck out a tumor that's weirdly shaped, or one that's stuck to another tumor?" said study co-author Ian Winters, a graduate student in Winslow's lab. "We needed a better way to quantify tumor sizes."

The solution came from an unexpected source. Petrov, an evolutionary biologist, had been working with Stanford colleagues to develop DNA barcoding as a way of investigating rapid evolution in yeast. When Petrov learned about the experiments in Winslow's group, he thought that the technique might also work in mice.

"Dmitri's the sort of guy who has a lot of wild ideas, and at first we didn't think that what he was suggesting was possible," Winslow said. "But after we thought about it for a couple of days, we realized that, well, actually, maybe we can do that."

Counting barcodes

Petrov's idea was to attach short, unique sequences of DNA to individual tumor cells inside mice lungs. Each sequence functions **See CANCER, page 3**

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STANFORD MEDICINE

Timing of stress-hormone pulses controls weight gain, study says

By Rosanne Spector

PAUL SAKUMA

Mary Teruel is the senior author of a study that found that rising and falling levels of hormones known as glucocorticoids can affect weight gain.

New research provides the first molecular understanding of why people gain weight due to chronic stress, disrupted circadian rhythms and treatment with glucocorticoid drugs: It's all in the timing of the dips and rises of a class of hormones called glucocorticoids — predominantly the "stress hormone" cortisol, according to a new study by School of Medicine researchers.

The research suggests new strategies to reduce weight gain by controlling the timing of hormonal pulses, said Mary Teruel, PhD, assistant professor of chemical and systems biology and senior author of the study, which was published online April 3 in *Cell Metabolism*.

"It explains why treatments with glucocorticoid drugs, which are often essential for people with rheumatoid arthritis and asthma to even function, are so linked with obesity, and it suggests ways in which such treatments can be given safely without the common side effects of weight gain and bone loss," she said.

Fat cells normally turn over at a rate of 10 percent per year; they die and are replaced by newly differentiated fat cells. What has long fascinated Teruel is how we stay at this rate, and the mystery of what flips the switch that leads to weight gain.

"Now we know the circadian code that controls the switch, and we've identified key molecules that are involved," Teruel said.

The team found that fat-cell maturation ramps up if the trough in exposure to glucocorticoids lasts less than 12 hours.

Teruel and her team made these findings during their effort to identify the molecular mechanism that precursor fat cells use to sense and filter out short pulses and normal oscillations of glucocorticoids.

The 24-hour hormone cycle

A healthy person's level of glucocorticoids rises and falls in a circadian 24-hour cycle, peaking around 8 a.m., dropping to its lowest around 3 a.m. the next day, and then rising back to its peak about five hours later. The rise is a wake-up signal that gets us moving and turns on our appetites. The glucocorticoid levels in our bloodstream are also increased by stress — short spikes are induced by short-term stress, such as exercise, and sustained levels are caused by chronic stress.

Researchers have long known that glucocorticoids trigger precursor cells to convert to fat cells, and that our fat tissue contains a huge excess of precursor cells that could convert, given the right signals. Under healthy conditions, less than 1 percent of a person's precursor fat cells are converting into fat cells. This low rate of conversion is essential for replacing damaged mature cells and for renewing and maintaining healthy fat tissue.

Hence Teruel's puzzlement: "So what stops normal, healthy daily increases in our glucocorticoid levels due to circadian rhythms and healthy short-term stresses from causing all our precursor cells to convert into fat cells? Why aren't we drowning in fat every time glucocorticoid levels go high in the morning due to normal circadian rhythms or when our glucocorticoid levels spike when we exercise or go from a warm building out into the cold? And why is losing the normal rhythm of glucocorticoid secretion — such as in conditions of chronic stress, jetlag and sleep disruption in shift-workers — so linked to obesity?"

The timing of glucocorticoid pulses had not been studied before, but Teruel thought it might offer the answer.

In the first of the series of experiments, graduate students Zahra Bahrami-Nejad and Michael Zhao, co-lead authors of the study, worked around the clock to expose precursor fat cells to glucocorticoids in carefully timed pulses over the course of four days, alternately bathing the petri-dish-grown cells in fluids with and without glucocorticoids and assuring that the total exposure to the hormone remained the same. They stained and imaged the cells so they could count how many of the precursor cells matured into fat cells. They found that one pulse of glucocorticoids lasting 48 hours led most of the cells to differentiate, while shorter pulses with at least 12 hours between them resulted in minimal differentiation.

To uncover how the precursors are able to sense the duration of the hormonal pulses and filter out short pulses, the researchers used single-cell live imaging to track PPAR-gamma protein levels in thousands of individual cells over several days while the precursors became fat cells. PPAR-gamma is a protein that correlates with the fat cell's maturity: When PPAR-gamma levels increase to a certain threshold level in a fat precursor cell, the precursor cell will convert in to a fat cell. Leading up to this experiment, Bahrami-Nejad had worked for about two years using CRISPR gene-editing technology to attach a fluorescent probe to all of the PPAR-gamma proteins the precursor fat cells produced. By measuring the fluorescence, she and Zhao were able to quantify levels of PPAR-gamma produced in the cells, which enabled them for the first time to watch individual cells convert from precursor cells into fat cells as it happened.

Relying on two types of feedback

The researchers' experiments and computer modeling indicated that the system must rely on two types of positive feedback — fast and slow — to enable precursor cells to ignore the normal rise and fall of glucocorticoids, as well as short daytime pulses, yet respond to long pulses. Their work had previously found that a protein called CEBP-alpha provides fast positive feedback — meaning PPAR-gamma activates CEBP-alpha, which in return activates PPAR-gamma, the cycle playing out over three hours. Additional studies identified a protein called FABP4 as a key slow positive-feedback regulator of PPAR-gamma. In this feedback loop, which takes 34 hours, PPAR-gamma activates FABP4, which in return activates PPAR-gamma. This allows PPAR-gamma to continue to build up in response to long pulses, despite its tendency to degrade.

As a final step, they explored whether the circadian code works in living animals. In a 21-day study in mice, the researchers found that loss of the normal circadian rhythm for glucocorticoids led to a doubling of the animals' fat mass. To carry out this experiment, postdoctoral scholars and study co-authors Stefan Tholen, PhD, and Devon Hunerdosse, PhD, raised glucocorticoid levels by implanting mice with pellets that contained glucocorticoids. They compared the weight of these mice to the weight of mice in groups implanted with pellets lacking the hormone. Though all the mice ate the same amount, only those implanted with glucocorticoids gained weight. The doubling of their fat mass was due to both the creation of new fat cells and the growth of existing fat cells.

They also found that no increase in fat occurred as long as they boosted glucocorticoids, delivered by injection, only during the normal circadian peak times — even if they increased peak glucocorticoid levels fortyfold.

The research has implications for controlling weight gain in humans, Teruel said. "Yes, the timing of your stress does matter. Since conversion of precursor cells into fat cells occurs through a bistable switch, it means you can control the process with pulsing. Our results suggest that even if you get significantly stressed or treat your rheumatoid arthritis with glucocorticoids, you won't gain weight, as long as stress or glucocorticoid treatment happens only during the day. But if you experience chronic, continuous stress or take glucocorticoids at night, the resulting loss of normal circadian glucocorticoid oscillations will result in significant weight gain," she said.

The link between food and glucocorticoids is not well-understood, Teruel said. Some of her newer experiments aim to understand how food, insulin and glucocorticoids are related.

Other Stanford co-authors of the study are former postdoctoral scholar Karen Tkach, PhD; former visiting scholar Sabine van Schie, PhD; and graduate student Mingyu Chung.

The research was supported by Stanford Bio-X, the National Institutes of Health, the DFG German Research Foundation and the American Heart Association.

Stanford's Department of Chemical and Systems Biology also supported the work. ISM

Cancer

continued from page 2

as a heritable genetic barcode, and as each cancer seed cell divides, growing into a tumor, the number of barcodes also multiplies.

Now, instead of having to painstakingly cut out individual tumors, the scientists could take an entire cancerous lung, grind it up, and then use high-throughput DNA sequencing and computational analysis to precisely determine how big a tumor was by counting how often its barcodes popped up. By tallying different barcodes, the scientists could compare tumor sizes much more quantitatively than was previously possible.

Genetic diversity

"This is 10 steps forward in our ability to model human cancer," Petrov said. "We can now generate a very large number of tumors with specific genetic signatures in the same mouse and follow their growth individually at scale and with high precision. The previous methods were both orders of magnitude slower and much less quantitative."

The combination of CRISPR-Cas9 and DNA barcoding could allow scientists to replicate in the lab the kind of genetic diversity observed in cancer patients. "It gets around this fear of the complexity of cancer," Winters said. "We've known for decades that human tumors are extremely complex and different from patient to patient, but how do you actually recreate that so you can study it? It's not by doing it one at a time. Now, we can model 30 different genetic variations of a cancer simultaneously."

One striking finding from the team's mapping study is that many tumor-suppressor genes are context-dependent — that is, they only affect cancer growth in the presence or absence of another gene. "We are now in a good position to understand how key cancer drivers interact with each other, and why tumors with the same mutations sometimes grow to be very large and sometimes not," McFarland said.

The team's hybrid technique could also prove valuable for cancer-drug testing. Pharmaceutical companies could test a drug on thousands of tumor variations simultaneously to see which ones respond to treatment and, just as importantly, which ones don't.

"We can help understand why targeted therapies and immunotherapies sometimes work amazingly well in patients and sometimes fail," Petrov said. "We hypothesize that the genetic identity of tumors might be partially responsible, and we finally have a good way to test this."

Petrov is an affiliate of the Stanford Woods Institute for the Environment. Winslow is a member of the Stanford Cancer Institute and the Stanford Neurosciences Institute. Both are members of Stanford Bio-X.

Other Stanford co-authors are postdoctoral scholar Jose Seoane, PhD; former postdoctoral scholar Jennifer Brady, PhD; and Christina Curtis, PhD, assistant professor of oncology and of genetics.

A researcher at the Massachusetts Institute of Technology also contributed to the work.

The study was supported by the National Science Foundation, the National Institutes of Health, Stanford Graduate Fellowships, the Stanford Cancer Systems Biology Scholars Program, Susan G. Komen and the Stanford Cancer Institute.

Stanford's departments of Genetics, of Pathology and of Biology also supported the work. ISM

Researchers engineer yeast to manufacture complex medicine

By Bruce Goldman

Stanford bioengineers have figured out a way to make noscapine, a non-narcotic cough suppressant that occurs naturally in opium poppies, in brewer's yeast.

The researchers inserted 25 foreign genes into the one-celled fungus to turn it into an efficient factory for producing the drug. Many of the inserted genes came from the poppy, but several came from other plants and even from rats. All those genes were recipes for enzymes: protein machines that, working together, can build complex substances from simple starting materials.

The researchers also modified some of the plant, rat and yeast genes, as well as the medium in which the yeast proliferates, to help everything work better together. The result was an 18,000-fold improvement in noscapine output, compared with what could be obtained by just inserting the plant and rat genes into yeast.

"This is a technology that's going to change the way we manufacture essential medicines," said Christina Smolke, PhD, professor of bioengineering.

An additional hundredfold improvement will be necessary for commercial viability, she said, but much of that can be achieved by substituting large-scale bioreactors for simple laboratory flasks.

A paper describing the research was published online April 2 in the *Proceedings of the National Academy of Sciences*. Smolke is the senior author. Yanran Li, PhD, a former postdoctoral scholar who's now an assistant professor of chemical and environmental engineering at the University of California-Irvine, and postdoctoral scholar Sijin Li, PhD, share lead authorship.

Promise as a cancer drug

Noscapine's cough-suppressing capability was discovered in 1930. The drug has been widely used since the 1960s as a cough medicine throughout Asia, Europe and South America, as well as in Canada, Australia and South Africa. Preclinical trials indicate potential for noscapine as a cancer drug with less toxicity to healthy cells than currently available chemotherapies.

But the only viable source of noscapine is opium poppies. Many tons of noscapine are extracted annually from the plant, which takes a full year to mature. While noscapine itself is harmless, the poppies' illicit potential requires costly controls and restrictive regulations. The plants can be legally grown only in a concentrated geographical area. Half of all poppies produced for noscapine are in Australia, and the rest are mostly in India, France, Turkey and Hungary, making global noscapine output subject to local environmental events and to varying soil and nutrient conditions. In addition, naturally occurring noscapine must be thoroughly separated from numerous molecular companions, narcotic and otherwise, that don't occur in yeast.

The yeast Smolke's group bioengineered can spew out substantial amounts of noscapine in three or four days. The investigators achieved this result by stitching three separate sections of the noscapine biosynthesis pathway into a single yeast strain.

Initially, noscapine output was meager, Smolke said. "Traditionally, we've gotten our medicines from the natural world, mainly from plants. But the plants' molecular assembly lines have evolved to optimize the plants' survival, not to churn out buckets of one substance we humans want to get our hands on," she said. "Plus, we're putting them into our yeast strain, which is foreign turf. A yeast cell and a poppy cell have a lot in common, but in some respects they're as different as Earth and Mars."

Every enzyme catalyzes its own limited set of chemical reactions. So, the synthesis of complex chemicals requires a whole assembly line of different enzymes working in concert with one another, ideally with each enzyme in the production chain generating just enough of its given intermediate product to keep the next one busy. As with a factory conveyor belt, too little activity, or too much, at any point can jam up the line. Enzymes need energy supplies too, and some of them require the assistance of additional molecules that may abound in the organism they come from, but not necessarily in a yeast cell.

Soldiers on Mars

"It's as if we're grabbing a couple dozen soldiers from different units, deploying them on Mars, and telling each of them, 'Now, not only am I putting you on Mars, but I want you to get some serious work done here, and I want you to work with these other soldiers you haven't worked with before — many of them total strangers,'" Smolke said. "Good luck with that. We modified them to keep them in shape on this planet and to get along with one another better, and we nudged the yeast to help these enzymes grab the resources they need to get the job done."

That entailed, among other things, splicing in rat genes that direct the production of dopamine, a key intermediate in noscapine synthesis. Dopamine's production in plants is poorly understood, but because of dopamine's importance as a crucial chemical in the animal nervous system, the enzymes responsible for its production in mammals have been studied intensively.

The scientists used CRISPR, a gene-editing tool, to alter inserted genes so that the enzymes for which they coded would work most efficiently amid the exotic acidity, osmotic character and chemical composition of their new home. They also souped up the yeast's production of a chemical whose levels would have otherwise been too low to sustain robust noscapine production.

"We're no longer limited to what nature can make," Smolke said. "We're moving to an age where we can borrow nature's medicine-manufacturing processes and, using genetic engineering, build miniature living factories that make what we want."

Stanford's Office of Technology Licensing holds pending patents on intellectual property associated with the findings in this study.

Other Stanford study co-authors are former graduate student Aaron Cravens, PhD, and former postdoctoral scholars Kate Thodey, PhD, and Isis Trenchard, PhD, now both at Antheia.

The study was funded by the National Institutes of Health and Novartis Institutes for Biomedical Research.

Antheia Inc., a biotechnology company based in Menlo Park, California, that Smolke co-founded in 2015, has licensed the technology from Stanford and is now working to commercialize noscapine production in yeast. Smolke is Antheia's chief executive officer.

Smolke is an investigator at the Chan-Zuckerberg Biohub and a member of Stanford Bio-X and of the Stanford Neurosciences Institute. She also is a faculty fellow at Stanford ChEM-H.

Stanford's Department of Bioengineering, which is jointly managed by Stanford's School of Medicine and School of Engineering, also supported the work. **ISM**

ROD SEARCEY

(Above) Christina Smolke is the senior author of a study describing how brewer's yeast can be engineered to make noscapine, a plant-derived cough suppressant and potential anticancer drug. (Top left) Colonies of the noscapine-producing yeast.

In study, researchers probe the complex nature of concussions

By Nathan Collins

It seems simple enough: Taking a hard hit to the head can give you a concussion. But in most cases, the connection is anything but simple, according to a new study led by researchers at Stanford University.

Combining data recorded from football players with computer simulations of the brain, the researchers found that concussions and other mild traumatic brain injuries seem to arise when an area deep inside the brain shakes more rapidly and intensely than surrounding areas. But they also found that the mechanical complexity of the brain means there is no straightforward relationship between different bumps, spins and blows to the head and the likelihood of injury.

A paper describing the findings was published March 30 in *Physical Review Letters*. David Camarillo, PhD, assistant professor of bioengineering, is the senior author. Lead authorship is shared by former postdoctoral scholars Mehmet Kurt, now an assistant professor of mechanical engineering at Stevens Institute of Technology., and Kaveh Laksari, now an assistant professor of biomedical engineering at the University of Arizona.

SAUL BROMBERGER AND SANDRA HOOVER

David Camarillo is the senior author of a study that found that in cases of concussion, an area deep in the brain called the corpus callosum shakes more rapidly than the surrounding areas.

"Concussion is a silent epidemic that is affecting millions of people," Kurt said. Yet exactly how concussions come about remains something of a mystery.

"What we were trying to do is understand the biomechanics of the brain during an impact," Kurt said. Armed with that understanding, engineers could better diagnose, treat and hopefully prevent concussion, he said.

Shaking the brain

In previous studies, Camarillo's lab outfitted 31 college football players with special mouth guards that recorded how players' heads moved after an impact, including a few cases in which players suffered concussions.

Laksari and Kurt's idea was to use that data, along with similar data from NFL players, as inputs to a computer model of the brain. That way, they could try to infer what happened in the brain that led to a concussion. In particular, they could go beyond relatively simple models that focused on just one or two parameters, such as the maximum head acceleration during an impact.

The key difference between impacts that led to concussions and those that did not, the researchers discovered, had to do with how — and more importantly where — the brain shakes. After an average hit, the researchers' computer model suggests the brain shakes back and forth around 30 times a second in a fairly uniform way; that is, most parts of the brain move in unison.

In injury cases, the brain's motion is more complex. Instead of the brain moving largely in unison, an area deep in the brain called the corpus callosum, which connects the left and right halves of the brain, shakes more rapidly than the surrounding areas, placing significant strain on those tissues.

Further complications

Concussion simulations that point to the corpus callosum are consistent with empirical observations: Patients with concussions do often have damage in the corpus callosum. However, Laksari and Kurt emphasize that their findings are predictions that need to be tested more extensively in the lab, either with animal brains or human brains that have been donated for **See CONCUSSION, page 6**

Boy undergoes complex liver, kidney transplants — all before age 3

By Julie Greicius

Dane Conrads was in excellent health when he was born, almost five weeks early, in April 2014 in San Francisco. But after being circumcised, Dane started bleeding, and it wouldn't stop.

For Dane's parents, A.J. and Ted Conrads, it was an unexpected shock. "A blood test showed that his liver enzymes were through the roof, which was a sign that his liver was failing," A.J. recalled.

An ambulance rushed Dane to Lucile Packard Children's Hospital Stanford. "It was all hands on deck," A.J. said.

Janene Fuerch, MD, clinical assistant professor of neonatology at Stanford, was one of the neonatal intensive care unit fellows during Dane's first several weeks at Packard Children's. "He was in fulminant liver failure, and we knew he was most likely going to die. Neonates in severe liver failure often don't survive," she said.

Ultimately, he would undergo two separate transplants before his third birthday. He was fortunate to be treated at Packard Children's, a longtime leader in pediatric solid-organ transplant. In 2017, the hospital led the way in pediatric transplant volume and outcomes nationwide, performing 117 pediatric organ transplants. Over the past five years, Packard Children's has performed more pediatric liver and kidney transplants than any other U.S. hospital.

To help him survive his failing liver, Dane's doctors stabilized him with several daily blood transfusions and continuous medical support. Over the next 10 days, rounds of testing revealed that Dane was infected with an enterovirus, a relative of the polio virus.

'A desperately ill little guy'

"He was really a desperately ill little guy," said William Benitz, MD, professor of neonatology and Dane's attending physician in the NICU. "He demonstrated how sick a vulnerable baby can get from what would be a routine, ho-hum, everyday virus for most of us."

In a premature baby like Dane, enterovirus can cause liver failure, which can lead to brain damage and heart failure. Enterovirus has no available medical cure, so Dane's own immune system had to fight the disease.

The next six weeks were a harrowing, daily effort to keep Dane alive and help him grow healthy enough — and large enough — to receive a liver transplant. "We knew this was a stretch. He would be the smallest transplant the team had ever done," Fuerch said. "But he wasn't giving up, so we weren't going to either."

The team has a track record of succeeding with unusually challenging transplants. In 2017, 40 percent of Packard Children's liver-transplant recipients weighed less than 40 pounds, making it the national leader in transplanting babies and small children. The hospital also had much shorter mean wait times than most transplant centers: 2.2 months, compared with 13.5 months nationwide.

And Dane needed a new liver quickly. Even as his care team worked to stabilize his blood levels every day, his failing liver was not doing its job of clearing his blood of protein byproducts like ammonia. This meant he needed continuous hemodialysis, which circulated his blood to clean it externally and return it to his body. "We had to balance the risks of bleeding, clotting and infection and work to optimize his nutrition," said Cynthia Wong, MD, clinical associate professor of pediatric nephrology and medical director of chronic dialysis. "With his multiorgan failure, this was the only option to save his life."

CONRADS FAMILY

Dane Conrads, who underwent two organ transplants at Lucile Packard Children's Hospital Stanford, with his mother, A.J. Conrads.

'Tremendous moment of success'

"When the interventional radiologist put in a dialysis catheter, it was a tremendous moment of success," said Waldo Concepcion, MD, professor of surgery and chief of pediatric kidney transplantation. "Being able to dialyze him so the medical team could stabilize him was very, very critical to his survival."

> **"It was a completely innovative process of doing the kidney transplant."**

In the early hours of May 23, 2014, 6-week-old Dane, weighing just under 5 pounds, received his new liver from a surgical team led by Carlos Esquivel, MD, PhD, professor of surgery and chief of the division of transplantation, and Concepcion.

About six weeks after Dane's surgery and his slow, rocky recovery, A.J. and Ted were finally able to pick him up and hold him for the first time since his birth. But soon after his new liver stabilized, Dane's kidneys failed. He now needed peritoneal dialysis to do the work of his kidneys.

On Oct. 8, after six months in the hospital, A.J. and Ted were able to take Dane home, where he would need 11 hours of peritoneal dialysis each day until he could receive a kidney transplant.

Although they were concerned about their son, the family knew of Packard Children's outstanding kidney-transplant track record. In 2017, the program performed 46 pediatric kidney transplants, as well as nine transplants in patients age 18 or older, making it a national leader in kidney-transplant volume. Patients come from across the Western United States and even internationally to benefit from the program's expertise.

A.J. hoped to be a living kidney donor for Dane. But Dane needed a perfectly sized kidney, which could only come from a deceased donor. "The odds were stacked against Dane both in terms of the complexity of the anticipated surgery and the scarcity of potential donor kidneys," Ted said.

On April 7, 2017, one day before Dane's third birthday, Concepcion and Amy Gallo, MD, assistant professor of surgery, performed Dane's pioneering kidney transplant.

"He was tiny, but we modified and tailored his own kidney vein to be able to drain the new kidney," Concepcion said. "It was a completely innovative process of doing the kidney transplant using only what the patient had available, which was that one vein."

It was one of the most complicated of the kidney transplants performed at Packard Children's in 2017, though it was not unique: The team also transplanted two other children who had been referred from outside California due to challenging vascular access, as well as a patient who needed a second kidney transplant after becoming immunologically sensitized to the first transplanted organ.

Within 24 hours of his kidney transplant, Dane showed signs of dramatic improvement. He was discharged after 10 days.

Today, Dane loves playing with his little brother, Carter. "He's just really happy now. He's super-social and loves his toys and going to music class," A.J. said. "Finally, after three years, we're feeling relaxed — like, OK, he's going to be OK." ISM

Mixed-media mosaics of the human body, inspired by *Frankenstein*

By Kris Newby

Third-year medical student Nick Love, PhD, combined his passion for art, literature and medicine in creating an art exhibit at the Li Ka Shing Center for Learning and Knowledge that commemorates the 200th anniversary of Mary Shelley's novel Frankenstein.

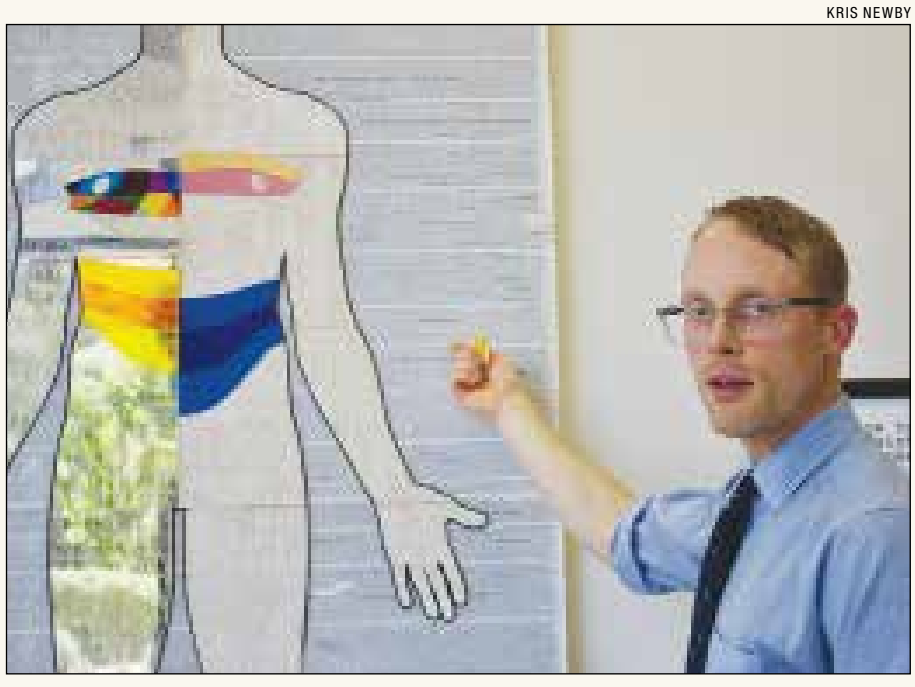
While the fictional Dr. Frankenstein stitched his monster together from cadaver parts, Love built his monsters with plastic, wood, precision laser cutters and pages ripped from an old copy of the novel.

"My inspiration began when I started thinking about skin as the canvas of the human body," said Love, who has an interest in dermatology.

Love drew the outline plans for his Frankenstein creations with software, using the shape of the human form in an "anatomic position" — arms out to the side, palms facing front — and then inscribed each with three sets of anatomy lines that he learned as a medical student.

The dermatome lines map skin regions linked to specific branches of the nervous system. The Blashko lines show how skin fuses together during embryonic development. And the Langer lines delineate differing tension forces over the surface of the skin, useful information in deciding how to orient a surgical incision and closure. When he layered the lines on top of the monster templates, they created pleasing shapes that he then inlayed with a playful assortment of materials and colors.

KRIS NEWBY



Medical student Nick Love used plastic, wood, precision laser cutters and pages from the novel *Frankenstein* to create pieces for an art exhibit at the Li Ka Shing Center for Learning and Knowledge.

Two of his 8-foot-tall mosaics were mounted on top of the complete text of Shelley's novel, which he laser-etched on the surface of metal, wood and acrylic-mirror sheets. It took months of precision laser cutter time and the use of shop resources at the Stanford Product Realization Lab to complete this artwork. He said these two large assemblages symbolize the layers of biomedical knowledge that have occurred in the 200 years since Frankenstein was published.

Love's monstrous creations, 32 in total, will be joined by other artistic interpretations of Frankenstein at the International Health Humanities Consortium: Frankenstein's 200th on April 20-22 at the Li Ka Shing Center.

His work was supported by the Stanford Medicine and the Muse Program's Frankenstein@200 Initiative and by the Ben and A. Jess Shenson Funds at Stanford.

Love said his Frankenstein artwork is available for sale, and that all proceeds will go a nonprofit foundation that supports children with chronic skin conditions.

To see more of Love's work, visit http://love-art-science-medicine.com. ISM

Plan

continued from page 1

Laboratory, which has put Stanford at the forefront of this new technology — an imaging technique that fires electrons at proteins frozen in solution to determine their structure — and which is being used by a number of School of Medicine faculty members.

For patient care, the plan aims to address rising costs while streamlining the patient experience and making it highly individualized. Entwistle cited the new Clinical Genomics Program, which was officially launched March 22, as an example of this personalized approach to care. The center uses a technology known as whole-exome sequencing to diagnose adults and children with undiagnosed genetic illnesses.

Embracing digital technologies

The framework envisions greater reliance on digital technologies, which have affected every aspect of society and the economy but have had little impact thus far in the health care sector, Minor said.

"We have the opportunity to lead the digital transformation of health and health delivery," he told the crowd.

To spur progress, Stanford Medicine plans to create a digital health and innovation hub, where faculty can receive help in bringing new ideas to fruition. The resource center will offer mentoring and feedback and help streamline the process of bringing innovations to life, radiology professor Rusty Hoffman, MD, said in another video shown at the meeting.

The creation of the new integrated strategic plan has followed much the same process Lucile Packard Children's Hospital used two years ago in devising its own strategic blueprint.

"The vision we created for Lucile Packard is to keep it simple and have a mechanism to communicate it to the rest of the enterprise," Dawes said in the video. "I'm glad Stanford Medicine has adopted the same framework we used."

The plan also will be aligned with the university's long-range plan, which is currently in development. Minor noted that he and university Provost Persis Drell, PhD, will present the two plans together at an April 4 town hall meeting.

The integrated strategic plan is a dynamic initiative that could change over time. The leaders encouraged continued feedback and participation on the part of faculty and staff.

They are scheduled to present the plan to the boards of directors of Stanford Health Care and Lucile Packard Children's Hospital in April and then to the university's board of trustees in June. **ISM**

ROD SEARCEY

More than 400 faculty, staff and students assembled March 23 to hear Stanford Medicine leaders lay out the principles of an integrated strategic plan aimed at aligning the goals and priorities of the medical school and hospitals.

Provost and dean: Stanford Medicine's strategic plan complements university's

The key pillars of Stanford Medicine's integrated strategic plan — value-focused, digitally driven and uniquely Stanford — overlap with the goals of the university's long-range planning process, Lloyd Minor, MD, dean of the School of Medicine, said April 4 at a town hall meeting in the Clark Center auditorium.

The lunchtime event drew about 125 members of the Stanford Medicine community to hear Minor and Provost Persis Drell, PhD, present updates and answer questions about the long-range planning process. Drell noted that the university's process began about a year ago with a goal to answer the question: What do we want Stanford to be one to two decades from now?

"You might say things are great today," Drell said. "But we know that the great research university is going to look different 10 to 20 years from now. We have to change in order to be even more relevant in the decades to come."

The university is "still making the sausage," as Drell put it, referring to the ongoing effort to review and synthesize the input from community members. That input was initially handled by four steering groups: one focused on research, one on education, one on the university community and one on Stanford's engagement beyond the university. University leaders will present the findings to the board of trustees today; they also plan to share the findings with the larger campus community on May 15.

The university began its planning process by asking faculty, staff and students to submit ideas. "We had over 2,800 of those," Minor said. "Over 600 of those related to biomedicine. There are some themes that emerged. Those themes will be incorporated into one of the areas of the university's long-range plan called 'Life and Health.'"

Stanford Medicine's plan is in step with the evolving goals of the university, Minor said. The goal to be digitally driven, for example, is not restricted to data about human health but also relates to the ways in which modern biomedical research is conducted, he said. "Today, a third or more of the School of Engineering faculty are focused on biomedical problems, and the statistics faculty and other quantitatively based disciplines have faculty now drawn to biomedical problems," he said. "One of the main reasons is that biology has grown up as a science, and is now firmly a quantitative science. Therefore, people whose backgrounds are in quantitative approaches to science are now attracted to study biological and biomedical problems."

After their opening remarks, Drell and Minor opened the floor for questions and discussion. Some of the topics raised were how to improve sustainability; how staff on individual units and departments can participate in the planning process; how to improve relationships with the city and county governments; how to further enhance Stanford's already-strong culture of collaboration; and how to develop a more diverse community — not only in recruiting, but in fostering an environment where everyone is comfortable.

A clear message throughout the discussion — and, according to Drell and Minor, throughout the planning process so far — was the energy and desire of the members of the university, including Stanford Medicine, to make meaningful contributions to the world, and to continue to make Stanford better.

Learn more about the university's long-range planning process at https://planning.stanford.edu. **ISM**

Fitness

continued from page 1

in Finland.

Grip tests, accelerometers and more

To determine the fitness and activity levels of participants, researchers used data previously collected from 482,702 participants who underwent grip-strength tests correlating with overall body strength; answered questions about their levels of physical activity; wore accelerometers on their wrists for seven days; and took stationary-cycling tests. Genetic data from 468,095 of the participants was also used in the study.

Erik Ingelsson

Researchers found across the board that higher levels of fitness and physical activity were associated with lower levels of several negative cardiovascular outcomes, including coronary artery disease, stroke and atrial fibrillation.

Among those considered at high genetic risk for heart disease, high levels of cardiorespiratory fitness were associated with a 49 percent lower risk for coronary heart disease and a 60 percent lower risk for atrial fibrillation compared with study participants with low cardiorespiratory fitness.

For participants deemed at intermediate genetic risk for cardiovascular diseases, those with the strongest grips were 36 percent less likely to develop coronary heart disease and had a 46 percent reduction in their risk for atrial fibrillation compared with study participants who had the same genetic risk and the weakest grips. Researchers determined various levels of genetic risk according to measurements based on discoveries from genomewide association studies, the most common study design to discover genetic variation associated with disease.

'It can make a difference'

Given little has been known about the risk-modifying effects of exercise in individuals with increased genetic risk of cardiovascular disease, these results could have important ramifications for public health the study said.

"This is important because of how we advise our patients," Ingelsson said. "It's basically indicating that you can make some lifestyle changes, be more physically active and it can make a difference to your long-term health."

A researcher at Uppsala University in Sweden contributed to the study.

The research was supported by the National Institutes of Health, the Knut and Alice Wallenberg Foundation, the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research and the Emil Aaltonen Foundation.

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

Concussion

continued from page 4

scientific study. "Observing this in experiments is going to be very challenging, but that would be an important next step," Laksari said.

Perhaps as important as physical experiments are additional simulations to clarify the relationship between head impacts and the motion of the brain — in particular, what kinds of impacts give rise to the complex motion that appears to be responsible for concussions and other mild traumatic brain injuries. Based on the studies they have done so far, Laksari said, they know only that the relationship is highly complex.

Still, the payoff to uncovering that relationship could be enormous. If scientists better understand how the brain moves after an impact and what movement causes the most damage, Kurt said, "we can design better helmets, we can devise technologies that can do on-site diagnostics, for example in football, and potentially make sideline decisions in real time," all of which could improve outcomes for those who take a nasty hit to the head.

The study was supported by the Child Health Research Institute, the Lucile Packard Foundation for Children's Health, Stanford's Clinical and Translational Science Award and the Thrasher Research Foundation.

Stanford's Department of Bioengineering, which is jointly managed by the School of Medicine and the School of Engineering, also supported the work. **ISM**

OBITUARY

Eric Shooter, founding chair of neurobiology, dies at 93

By Bruce Goldman

Eric Shooter, PhD, professor emeritus of neurobiology at the School of Medicine and founding chair of that department, died March 21. He was 93.

Shooter was internationally acclaimed in the field for his work on the structure and mechanisms of neurotrophins, the proteins that keep nerve cells alive. He was the first to robustly characterize the neurotrophin known as nerve growth factor, which plays a key role in regenerating lost or damaged nerve cells. The discovery could someday make it possible to regrow nerves for those who have suffered spinal cord injuries, or to reverse the nerve degeneration that leads to conditions such as Alzheimer's and Parkinson's diseases.

"Eric Shooter was a leading light in the study of protein factors that support the growth and survival of nerve cells during embryonic and fetal development, and in disease," said Stanford President Marc Tessier-Lavigne, PhD, who is also a neuroscientist. "He was also a kind and supportive mentor to generations of young neuroscientists. He will be sorely missed."

"The neuroscience community and Stanford Medicine have lost a major contributor with the passing of Eric Shooter," said Lloyd Minor, MD, dean of the Stanford School of Medicine. "His groundbreaking research paved the way for the modern-day science of nerve growth factors and the remarkable role these proteins play in sustaining nerve cells."

Native of England

Shooter was born on April 18, 1924, in a small village north of Nottingham, England. After spending his childhood in the nearby town of Burton-on-Trent, where his family moved shortly after his birth, Shooter attended the University of Cambridge, where he studied chemistry, earning a bachelor's degree in 1945, a master's degree in 1946 and a PhD in 1949.

Eric Shooter

He came to the United States that year with his wife, Elaine, for a postdoctoral fellowship at the University of Wisconsin-Madison. "We arrived in New York with $10 each in our pockets," the maximum amount the British government would allow its citizens to export at that time, Shooter said in a 2002 interview. "You can do these things when you're 24."

At Madison, Shooter immersed himself in protein chemistry, imbibing techniques for separating large proteins. A year later, he returned to the United Kingdom to work in a British nonprofit and then to serve as a lecturer in biochemistry at University College London. There, Shooter made important discoveries about the biochemical genetics of hemoglobin.

In 1961, he was selected as a U.S. Public Health Service International Fellow with the Department of Biochemistry at Stanford's School of Medicine. He was appointed associate professor of genetics in 1963 and, in 1968, promoted to full professor of biochemistry and of genetics. Between 1972 and 1982, he chaired the school's doctoral program in neurosciences. In 1975, he became the founding chair of the Department of Neurobiology, a position he held through 1987.

'The curator of my career'

Those who worked with Shooter recalled that he was a gentle, avuncular figure who never failed to treat others with warmth and generosity.

Carla Shatz, PhD, professor of biology and of neurobiology and the director of Stanford Bio-X, was one of Shooter's early recruits to the nascent neurobiology department. "Eric hired me for my first faculty position in 1978," she said. "As my mentor here, he taught me something important: to be gentle, to give back. His example was a reminder that you can be a great scientist and still support the careers of other young scientists. He was the curator of my career."

Shooter also recruited William Newsome, PhD, professor of neurobiology and director of the Stanford Neurosciences Institute, who first arrived at Stanford in 1988. "The first time we met, he made an overwhelmingly positive impression," Newsome said. "He was a fantastic, warm human being, as kind and considerate as a person could be."

Elaine Shooter was the department's financial administrator for many years, Newsome said. "Together, Eric and Elaine really built the department," he said, adding that the pair connected on a personal level with faculty, students and postdoctoral scholars and their families.

In 1964, at the suggestion of Nobel laureate Joshua Lederberg, PhD, then professor and chair of genetics, Shooter turned his attention to a newly discovered protein called nerve growth factor. Three years of intensive work resulted in myriad discoveries about this important substance, including the complex in which it's packaged, the sites where it's most active and how it gets there, and the workings of its receptors on nerve cells.

He also discovered the gene in mice underlying a group of diseases called the demyelinating peripheral neuropathies, in which the protective myelin covering on nerves breaks down and the nerves are unable to function properly. The diseases are similar to human neurological diseases, and the discovery laid the groundwork for understanding how nerves repair themselves.

The discovery that a neurotrophin called brain-derived neurotrophic factor enhances myelin formation took place in Shooter's laboratory the early 2000s. He retired in 2004. In all, his career spanned well over a half-century.

Shooter was a fellow of the Royal Society and the American Academy of Arts and Sciences. Among other honors, he won the Javits Neuroscience Investigator Award from the National Institute of Neurological Disorders and Stroke, and shared the 1995 Ralph W. Gerard Prize from the Society of Neuroscience with Swiss neuroscientist Hans Thoenen, PhD. The co-author of more than 100 journal articles, Shooter served as an editor of several journals, including the *Journal of Neurochemistry, Neurobiology, Journal of Biological Chemistry, Journal of Neuroscience* and *Neuron.*

A Tareytown, New York-based biotechnology company, Regeneron Pharmaceuticals, which Shooter co-founded in 1988, has met with success in the commercialization of a number of drugs. In 2014, Shooter donated $4 million from his equity holdings in Regeneron to Stanford in order to establish the Shooter Family Professorship, now held by Thomas Clandinin, PhD, professor and chair of neurobiology.

He is survived by a daughter, Annette Devost, of San Carlos, California; and two granddaughters, Michelle and Stephanie. ISM

Tobacco

continued from page 1

including tobacco, fewer than half of the brand-sponsored pages included such an "age gate."

"Clearly, there are a lot of policies with the laudable intent of keeping tobacco promotion and sales out of Facebook," said Robert Jackler, MD, professor and chair of otolaryngology-head and neck surgery and principal investigator of Stanford Research Into the Impact of Tobacco Advertising.

"These policies are voluntary, and they're a sign of Facebook's commitment to social responsibility. With some 2 billion users and an enormous volume of daily postings, Facebook has a daunting task of policing its content."

NORBERT VON DER GROEBEN

Several Facebook policies bar tobacco sales and promotion on the platform, but Robert Jackler and his team of researchers found brands and vendors marketing their products through unpaid content.

Jackler, the Edward C. and Amy H. Sewall Professor in Otorhinolaryngology, is the lead author of the study, which was published online April 5 in *The BMJ Tobacco Control.*

Jackler and his fellow researchers looked to Facebook for the study because younger people are more likely to begin using tobacco products, with the risk of becoming nicotine-addicted, and because youth tend to be more active on social media.

Marketing through unpaid content

The researchers searched for company-sponsored Facebook pages among 388 leading tobacco brands and found such pages for 108, including for more than half of the top 46 hookah tobacco brands and of the top 92 e-cigarette brands.

While the researchers identified pages for none of the 21 top traditional cigarette brands, they found that 10 of 14 online tobacco stores with company-maintained Facebook pages promoted popular cigarette brands, such as Marlboro and Camel, and included links to purchase them.

The researchers then evaluated the pages in the context of Facebook's content policies that mention tobacco.

The advertising policy, which applies to paid ads and commercial content, does not permit images of tobacco; however, 107 of the 108 company-sponsored pages included such imagery, the study found.

The commerce policy, which governs items, products and services sold on Facebook, prohibits the sale of tobacco and related paraphernalia. As recently as last summer, Facebook also specifically banned private individuals from buying, selling or trading tobacco products, but that provision had been removed by February 2018, the researchers found. Additionally, the advertising policy bars the promotion of tobacco product sales — for example, with language like "Buy cigarettes and e-cigarettes here today." But in their study, the researchers found purchase links on 58 of the brand-sponsored pages and sale promotion on 71 of them — including, in both cases, about three-quarters of the e-cigarette brands.

Minors and user-engagement strategies

On many of the pages, the researchers found a lack of safeguards meant to prevent access to minors. Several also showed evidence of strategies to interact with users, enable ongoing exposure to their brands and create online communities to promote tobacco products.

The platform's "page terms," which apply to all Facebook pages, require restricted access to people under 18 from pages promoting the private sale of tobacco products. According to the researchers, it was unclear what was meant by "private sale" and whether the policy would apply to the public sale of tobacco products by commercial entities. Regardless, the study found that a majority of the examined pages — 56 percent of the tobacco-brand-sponsored pages and 90 percent of the online vendors' pages — failed to incorporate measures to screen out underage consumers.

The study also examined the number of Facebook "likes" for each brand and vendor page. It found that 30 had accumulated 10,000 or more likes, with four of the pages counting more than 50,000 likes.

"From an advertiser's point of view, you want to make sure you've gotten someone's attention," Jackler said, "and the fact that they've responded approvingly means your message has gotten through with some potency."

Ultimately, he said, the study reveals loopholes within Facebook's tobacco-related policies that the company could potentially close.

"Our hope is that our study, by highlighting the degree to which tobacco marketers evade Facebook's intended restrictions, will encourage the company to make a renewed effort to implement its well-intentioned policies," Jackler said.

Other Stanford co-authors of the study are former intern Vanessa Li; undergraduate student Ryan Cardiff; and research associate Divya Ramamurthi.

The research was supported by Stanford Research Into the Impact of Tobacco Advertising. Stanford's Department of Otolaryngology also supported the work. ISM

Taubes commit $20 million to Lucile Packard Children's Hospital

By Jennifer Yuan

Tad and Dianne Taube have committed $20 million to Lucile Packard Children's Hospital Stanford to support the opening of the new main building, which welcomed its first patients last December.

The newly renamed Tad and Dianne Taube Pavilion (the south tower of the new main building) houses state-of-the-art operating rooms, imaging suites and intensive care units in a child-friendly environment.

This commitment will bring the couple's total giving to Packard Children's and the child health programs at the Stanford School of Medicine to more than $35 million. The Taubes now rank among the top five individual donors in Packard Children's 26-year history since the original founding gift from David and Lucile Packard.

"We believe that it's important to invest in the children of today, because they are our citizens and leaders of the next generation," said Tad Taube, chairman of Taube Philanthropies. "They should be given every opportunity to grow with optimum health — one of the foremost priorities of our philanthropies. We are privileged to support the remarkable new Lucile Packard Children's Hospital and other important health initiatives at Stanford which make a positive contribution for children and young adults."

Other initiatives the Taubes have funded in recent months include the Tad and Dianne Taube Youth Addiction Initiative, which addresses the treatment and prevention of addiction during adolescence (made possible by a $9.5 million gift); the Taube Stanford Concussion Collaborative, which advances education, care and research to protect children from concussions (a $5 million gift); and the Taube Pediatric Neurodegenerative Research Initiative, which funds research in neurodegenerative disease in children (a $1 million gift, plus a challenge match of $375,000).

"This commitment to Packard Children's Hospital aligns with our priority of providing the best resources for health care for the youth in our greater community," Dianne Taube said.

The Taubes' most recent gift will support the design, construction and purchase of equipment for Packard Children's 521,000-square-foot main building. The new building adds 149 patient beds for a total of 361, enabling the hospital to serve more patients than ever.

Construction continues on parts of the hospital. On the hospital's first and fifth floors, dedicated spaces for cancer and heart programs are being created. The surgery center, to open later this year, will feature six state-of-the-art operating suites, bringing the hospital's total to 13. Packard Children's original building, the west building, will be expanding its preeminent center for expectant mothers and babies.

"We planned every detail in our new hospital to provide the best care for children," said Dennis Lund, MD, interim president and CEO, and chief medical officer, of the hospital and Stanford Children's Health. "We are honored that Tad and Dianne Taube chose to make a difference in the lives of our patients and families through their visionary investments."

Philanthropic support played a key role in making the new hospital possible. The community donated $265 million for the new building and surrounding 3.5 acres of gardens and green space. **ISM**

SAUL BROMBERGER & SANDRA HOOVER PHOTOGRAPHY

The south pavilion of the Packard Children's Hospital will be named in honor of Bay Area philanthropists Dianne and Tad Taube.

Four School of Medicine faculty members appointed to endowed professorships

Four faculty members at the School of Medicine have been appointed to endowed professorships.

ELECTRON KEBEBEW, MD, professor of surgery, was appointed the Harry A. Oberhelman Jr. and Mark L. Welton Professor, effective Feb. 13. He is the chief of general surgery. He specializes in endocrine surgery with a research focus on identifying the genomic drivers of endocrine cancers, and on the development of precision methods to treat endocrine tumors based on genetics and imaging.

The professorship was created in 2012 by Edward and Liliane Schneider to honor Mark Welton, MD, who left Stanford in 2017. It was combined with a professorship created by the Department of Surgery to honor Harry Oberhelman, MD, the late Stanford professor emeritus of surgery, who served as chief of general surgery for more than 25 years. Edward Schneider is the former chairman of Triton Container International. Liliane Schneider works to support people with disabilities and to allow seniors to remain connected to their communities.

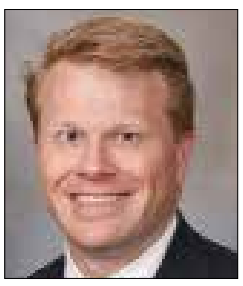
JON PARK, MD, professor of neurosurgery, was appointed the Saunders Family Professor, effective Dec. 5. He is the chief of spine neurosurgery and directs the spine research laboratory and the spine fellowship program. His clinical focus is on surgically and nonsurgically managing spinal disorders, and his research targets the underlying causes of spinal disc regeneration.

The professorship was created by Joseph and Sharon Saunders to support a faculty member in the Department of Neurosurgery, beginning with Park. Joseph Saunders held several CEO and other leadership positions in credit card companies, including Visa Inc., from which he retired in 2013. Sharon Saunders worked as a bank officer and restaurant manager.

TAIT SHANAFELT, MD, professor of hematology, was appointed the Jeanie and Stew Ritchie Professor, effective Dec. 5. He is the chief wellness officer and an associate dean of the School of Medicine, and he directs the Stanford Medicine WellMD Center. He specializes in physician well-being and its implications for quality of care. His clinical work and translational research focus on the treatment of patients with chronic lymphocytic leukemia.

Electron Kebebew

Jon Park



Tait Shanafelt

Gary Shaw

The professorship was created by Jeanie Ritchie in memory of her first husband, C. Stewart Ritchie, MD, a 1968 graduate of the School of Medicine, to support the director of the WellMD center. Jeanie Ritchie earned a bachelor's degree from the former School of Nursing at Stanford and a master's degree from the School of Education. She is the chair and former CEO of the corporate food service provider Guckenheimer, which she co-founded with her first husband.

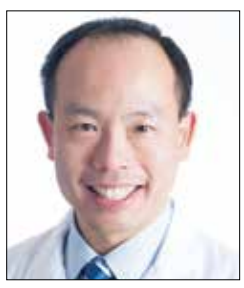
GARY SHAW, DrPH, professor of pediatrics, was appointed the NICU Nurses Professor, effective Dec. 5. His research interests include epidemiology of birth defects, nutrition during pregnancy and how the interactions between genes and the environment affect perinatal outcomes.

The professorship was created by an anonymous donor, who is an alumnus of the School of Medicine, to support a faculty member in the Division of Neonatal and Developmental Medicine in the Department of Pediatrics. It will be renamed for David K. Stevenson, MD, upon his retirement or departure from Stanford. Known for his work in neonatal jaundice and prevention of preterm birth, Stevenson is senior associate dean for maternal and child health and co-director of the Child Health Research Institute. **ISM**

OF NOTE

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

Kimberly Allison



Bill Chiu

Karl Deisseroth

Kevin Grimes

Lisa Knowlton

KIMBERLY ALLISON, MD, was promoted to professor of pathology, effective Oct. 1. She serves as director of breast pathology and program director of the anatomic and clinical pathology residency. Her research interests include the development of diagnostic standards and the identification of new diagnostic and therapy-related tumor markers in breast pathology.

BILL CHIU, MD, was appointed associate professor of surgery, effective Jan. 1. His research focuses on understanding and treating neuroblastomas, including using local drug delivery therapy.

KARL DEISSEROTH, MD, PhD, the D.H. Chen Professor and a professor of psychiatry and behavioral sciences and of bioengineering, was awarded the Frances & Kenneth Eisenberg Translational Research Prize from the University of Michigan Comprehensive Depression Center. The honor recognizes breakthrough research accomplishments in understanding and treating depression, bipolar disorder and related conditions. He received the $50,000 prize for his leadership in optogenetics, a technology that allows scientists to precisely manipulate nerve-cell activity in freely moving animals.

KEVIN GRIMES, MD, was promoted to professor (teaching) of chemical and systems biology, effective March 1. He is co-director of the SPARK Translational Research Program, which provides information and resources to researchers hoping to translate biomedical research discoveries into new treatments for patients.

LISA KNOWLTON, MD, was appointed assistant professor of surgery, effective Feb. 1. In addition, she was awarded the C. James Carrico, MD, FACS, Faculty Research Fellowship for the Study of Trauma and Critical Care by the American College of Surgeons. The one-year, $40,000 award, with the option of a one-year continuance, will allow her to pursue a project on the impact of policy on the quality of trauma care. Her research interests include translating disparities among surgical patients into health-policy interventions and reducing barriers in access to surgical care globally. **ISM**